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THE CONTROL AND COMPLETE REMISSION OF POLYCYTHEMIA VERA FOLLOWING THE PROLONGED ADMINISTRATION OF PHENYLHYDRAZIN HYDROCHLORID.*

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A conception of the history and the present status of the treatment of polycythemia vera by means of phenylhydrazin hydrochlorid may be obtained by reviewing the papers of Eppinger and Kloss,[7] Taschenberg,[16] Levi,[12] Owen,[14] Brown and Giffin,[5] Bryan,[6] Giffin and Conner,[10] and by the experimental studies of Allen and Giffin,[3] Allen and Barker,[2] and Huffman,[11] and by Giffin's summary.[9] These studies show that most patients aged less than 60 years with polycythemia vera, who are not in an advanced stage of the disease, can safely be given an initial course of phenylhydrazin in 0.1-gm. doses 2 or 3 times daily until a total dosage of from 3 to 4 gm. of the drug has been administered, or, if less than this dosage is required, until definite clinical evidence of active hemolysis presents itself. The drug in such dosage is cumulative in its action and hemolysis almost always continues for a week or 10 days following its withdrawal. During this initial treatment patients should be treated as though they were ambulatory, under hospital observation if possible, and every effort should be made to keep the circula-

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tion free and active. On the other hand, phenylhydrazin should be given cautiously, if at all, in cases with advanced arteriosclerosis and visceral lesions, in cases in which the patient is bedridden, in cases in which the history is suggestive of extensive preëxisting thrombosis, and in cases in which patients are aged more than 60 years. In certain such cases rapid hemolysis and fatal outcome[10] have occurred with small dosage.

The immediate problem of this paper is a consideration of the method of treatment best adapted to the control of polycythemia vera following the initial course of treatment. In some of the earlier cases the treatment was omitted completely after the initial course and resumed only when the polycythemic state became marked and symptoms became aggravated. This type of treatment had distinct disadvantages, especially because of the fact that the daily administration of phenylhydrazin requires close observation by the physician, and the patient must look forward to recurring periods of disability. It was recognized that an ideal method of treatment would be one which would maintain the patient in a more nearly normal condition so far as symptoms, erythrocyte count, and blood volume were concerned. By the method of trial and error it was finally found that the administration of from one to three 0.1-gm. doses of phenylhydrazin 1 day of each week, the dosage being varied chiefly according to the symptoms, was usually followed by satisfactory results. To our surprise it also developed that long-continued administration of the drug in this manner was followed in some of the cases by apparent complete inactivity of the disease, so far as the polycythemic state is concerned, with maintenance of normal blood count and blood volume for many months without phenylhydrazin. This has been a striking observation, clinically, in view of the extreme degree of polycythemia vera originally present in these cases. Fluctuation in the degree of polycythemia is a feature of the natural course of erythremia.[8] Anemia has occurred following gastrointestinal hemorrhage, and anemia with the appearance of immature cells has been described in advanced stages of the disease, but complete remission to normal blood count and normal blood volume with the patient in good health has been thought to be of rare occurrence.

Data on Cases Under Observation from 1925 to 1928. We are reviewing here chiefly the records of those patients with polycythemia vera who were given an inital course of phenylhydrazin under our observation during the years 1925, 1926 and 1927 in order to obtain a conception of the remote effects of treatment. It should be remembered that this was an experimental period, and the experience gained formed the basis for the foregoing and subsequent conclusions; phenylhydrazin was sometimes administered in cases that would now be regarded as unsuitable, and occasionally in excessive dosage.

From January 1, 1925, to January 1, 1928, 37 patients were seen whose condition was diagnosed as polycythemia vera. Of these 25 were given an initial course of treatment by phenylhydrazin hydrochlorid under our immediate observation. Four of the cases in which satisfactory data have been obtainable are presented in the form of brief abstracts. These data exemplify what may be accomplished by the more or less regular administration of small doses of phenylhydrazin over a period of several years. Notes on the remaining cases will be tabulated. Case 1 illustrates control following the initial course of treatment for 4 years by a small dosage 1 day each week. Case 2 illustrates control with a gradual reduction of dosage over a period of 4 years to less than 0.1 gm. each month. Case 3 illustrates absence of increased acquired tolerance to the drug on the recurrence of polycythemia. Case 4 illustrates complete remission without phenylhydrazin after 6 years of regular weekly dosage.

Abstracts of Cases. CASE 1.—A man, aged 50 years, came under our observation January 4, 1926. He had had polycythemia vera for approximately 4 years. He also had a duodenal ulcer. The spleen was moderately enlarged. Erythrocytes numbered 8,390,000 (estimated erythrocytes 8,330,000*); the percentage of erythrocytes by hematocrit was 75; whole blood volume was 205 cc. for each kilogram of body weight, and the viscosity of the blood was 20.6.

The patient was given 3.8 gm. of phenylhydrazin in 0.1-gm. dosage over a period of 18 days. Following this, he was much more active mentally and pain in the legs, troublesome before treatment, was much relieved. At this time, the erythrocytes numbered 4,440,000; the percentage of erythrocytes by hematocrit was 38; whole blood volume was 104 cc. for each kilogram of body weight, and the viscosity of the blood was 4.

After the initial course of treatment the patient was given 0.1 gm. of phenylhydrazin 3 or 4 times each week, with some variation in dosage, over a period of 4 years, during which time the symptoms were under satisfactory control and the erythrocyte counts never returned to their former high levels; they varied from 4,800,000 to 7,100,000, as a rule between 5,000,000 and 6,000,000. Following this, the patient took the drug irregularly, chiefly according to the recurrence of symptoms. After one year of this irregular dosage erythremia again developed, the erythrocytes reaching 8,260,000 in July, 1931. The patient stated at that time, however, that he felt confident from his former experience that he could again bring the condition under control by proper dosage. It is significant, however, in such an advanced case that the high blood volume could be kept under control for 4 years by the systematic weekly administration of small doses of phenylhydrazin.

CASE 2.—A man, aged 59 years, came under our observation April 20, 1927. He complained chiefly of flushed face, intolerance to heat, attacks of mental confusion, and loss of memory, which had existed for 3 years. Albuminuria had been present and an occasional erythrocyte was found in the urine. The concentration of urea in the blood was normal. The spleen was just palpable. Erythrocytes numbered 6,660,000 (estimated erythrocytes 7,220,000); erythrocyte percentage by hematocrit was 65; the whole blood volume was 162 cc. for each kilogram of body weight, and viscosity

* Based on the hematocrit reading compared with a normal of 45 per cent, and 5,000,000 erythrocytes. It assumes that the erythrocytes of polycythemia vera are normal in volume.

of blood was 10.6. The patient was given 3.6 gm. of phenylhydrazin in 0.1-gm. dosage over a period of 12 days. After treatment the erythrocytes numbered 2,290,000, unnecessarily severe anemia having been produced. The percentage of erythrocytes by hematocrit was 27; whole blood volume was 87 cc. for each kilogram of body weight. Superficial thrombosis developed in the legs, but there were no serious sequelæ. There were no symptoms except weakness and slight pain in the feet.

Over a period of $4\frac{1}{2}$ years the erythrocytes were enumerated monthly and careful records were kept of the phenylhydrazin taken. On the patient's recovery from the anemia caused by the initial course of treatment he began taking an average of 2 gm. of the drug each month, approximately 5 doses of 0.1 gm. each week. This amount was gradually decreased until in 1931, 4 years after the first examination, he was taking an average of 0.06 gm. each month. Beginning with May, 1930, the number of doses (0.1 gm.) each month exceeded 2 on only 1 occasion, and since January, 1931, an amount of phenylhydrazin in excess of 0.05 gm. each month was taken on only 2 occasions, when, respectively, 0.15 and 0.2 gm. were taken. In view of this it is probable that the amount of phenylhydrazin taken from May, 1930, to August, 1931, was not sufficient to cause hemolysis, but may have inhibited the production of erythrocytes. The patient's written statement concerning his experience is of special interest: it should be stated that a capsule contained 0.1 gm. of the drug. "It seems to me the tables show that continued administering of phenylhydrazin, gradually and in time reduces the activity of the system in the production of red corpuscles. The tables show that in the 7 months of 1927 after leaving St. Mary's Hospital I took an average of $20\frac{1}{2}$ capsules per month. In 1928, the average capsules taken decreased to $14\frac{1}{2}$ per month; in 1929 to $6\frac{7}{8}$ per month; in 1930 to $3\frac{1}{2}$ per month; and the first 9 months of 1931, an average of only $\frac{2}{3}$ capsule per month. It is true that decreasing dosage did not hold the red count down to the same average and the average of the blood counts increased in 1928, 1929, and 1930, yet the increase is negligible and in 1931, on the other hand, the average count decreases while the average monthly dose of medicine goes down to the least of any of the years." The average number of erythrocytes by monthly counts was 5,650,000 in 1928; 5,880,000, in 1929; 6,260,000, in 1930, and 5,930,000 in 1931.

Case 3.—A man, aged 50 years, came under our observation June 8, 1927. He complained chiefly of weakness and extreme exhaustion over a period of 2 years.

Erythrocytes numbered 6,810,000 (estimated erythrocytes 8,000,000); the percentage of erythrocytes by hematocrit was 73; the viscosity of the blood was 15, and the blood volume was 246 cc. for each kilogram of body weight. Over a period of 10 days, 4.4 gm. of phenylhydrazin was given, after which the erythrocytes numbered 4,940,000; the viscosity of the blood was 7.5, and the percentage of erythrocytes by hematocrit was 64. During treatment thrombosis of a superficial vein in the left leg developed. At this time, however, marked general improvement had occurred in the symptoms.

On dismissal, the patient was advised to take 3 doses (0.1 gm. each) 1 day a week, but through a misunderstanding he took this dosage 3 times a week. August 11, 1927, erythrocytes had become reduced to 2,400,000; several days previous to this count he had discontinued the use of the drug. October 15, 1927, the erythrocytes had risen to 6,500,000. The patient then took 0.1 gm. of the drug 3 times a week, and the erythrocytes fluctuated from 5,900,000 to 3,900,000 until February 1928. Again, on insufficient dosage, the number of erythrocytes increased to 6,300,000, and the patient took 0.2 gm. daily between April 6 and June 6, 1929, following which they became reduced to 3,500,000. Satisfactory control again was obtained by the administration of 3 or 4 doses a week of 0.1 gm. each until October, 1929,

when the erythrocytes had increased to 7,000,000, but were easily reduced again by an increased dosage of the drug.

The patient was in a satisfactory condition approximately 3 years following the initial course of treatment, although his record indicated that he had not satisfactorily determined the exact regular dosage which would keep his blood under constant control. The concentration of urea in the blood in June, 1928, was 14.4 gm. in each 100 cc. The return of phenolsulphonephthalein in the urine was 72 per cent. This was after the patient had been under treatment for 1 year.

Case 4.—A man, aged 56 years, came under observation August 16, 1927, giving a history indicative of at least 4 years of polycythemia vera.

Erythrocytes numbered 7,040,000 (estimated erythrocytes 7,550,000); the erythrocyte percentage by hematocrit was 68; the whole blood volume was 166 cc. for each kilogram of body weight, and the viscosity of the blood was 13. The spleen was slightly enlarged. Four and six-tenths grams of phenylhydrazin was given in 20 days. After treatment, erythrocytes numbered 4,450,000; erythrocyte percentage by hematocrit was 47; whole blood volume was 125 cc. for each kg. of body weight, and the viscosity of the blood was 5.2. The patient had obtained relief from vertigo, gastric distress, headache, and nervousness. Following the initial course of treatment, 0.2 or 0.3 gm. of phenylhydrazin was taken each week for approximately 9 months from November, 1927. During this time the maximal and minimal number of erythrocytes for each cubic millimeter of blood was 5,920,000 and 4,730,000, respectively. In only 4 of the 9 determinations during this time were the erythrocytes found to exceed 5,500,000 for each cubic millimeter of blood, and at no time did they fall below 4,500,000. The patient was entirely relieved of all symptoms and saw no reason for further reduction of the erythrocytes. There was a period of $2\frac{1}{2}$ months following this during which the patient did not take any phenylhydrazin.

The patient returned for examination July 2, 1928. Erythrocytes numbered 5,030,000; erythrocyte percentage by hematocrit was 59; whole blood volume was 141 cc. for each kilogram of body weight, and the viscosity of the blood was 5.4. The concentration of urea in the blood was normal and a test of hepatic function showed no retention of dye. He had been working regularly and feeling well.

In the next 18 months the patient took from 0.2 to 0.5 gm. of phenylhydrazin each month, an average dose of much less than 0.1 gm. each week, and from $\frac{1}{4}$ to $\frac{1}{2}$ as much as he had taken previously. During this period, 11 blood counts were made; the erythrocytes varied from 5,370,000 to 4,000,000, and there were no symptoms which seemed to be definitely attributable to polycythemia vera.

The patient was examined April 14, 1930, $2\frac{1}{2}$ years after the original treatment. Erythrocytes numbered 4,560,000; erythrocyte percentage by hematocrit was 55; whole blood volume was 92 cc. for each kilogram of body weight, and the viscosity of the blood was 5.8. There was some complaint of attacks of dizziness; otherwise, the patient felt well and had been working regularly.

From May 12, 1930, to August 27, 1931, a period of 15 months, the patient took almost inconsequential amounts of phenylhydrazin, and for the last 5 months of that period none was taken. Only twice did the erythrocytes exceed 5,000,000. At the present time the patient seems to be entirely relieved of polycythemia vera.

Comment on Abstracted Cases. In all of the abstracted cases response to the initial course of treatment was prompt and satisfactory. In Case 1, the patient, a man, aged 50 years, was able to maintain a satisfactory erythrocyte count, after the initial dosage,

for a period of 4 years on approximately 0.4 gm. of the drug each week. In Case 2, the patient, a man aged 59 years, was able gradually to reduce the dosage from an average of 0.5 gm. each week to 0.1 gm. each month over a period of 4 years; lately, even a smaller amount was taken each month. Finally, there was an absence of the polycythemic state and control of symptoms was completely effected. In Case 3, a man, aged 50 years, the patient's blood was brought under control with somewhat more difficulty than in the average case, but on each elevation of the erythrocyte count above normal there was no greater difficulty in reducing the blood count than was noted at the time of his initial treatment. There also was no evidence of impaired renal function 1 year after treatment was begun. In Case 4, a man, aged 56 years, the patient has never been markedly polycythemic since the initial course of treatment and the polycythemic state has been entirely absent since 1930. This result was obtained with a dosage which was gradually reduced from 0.3 gm. each week to complete withdrawal of the drug in the last five months. There was no evidence of reduced renal or hepatic function 1 year after treatment.

Of the 25 patients who received the initial course of treatment when under our observation, Cases 1 to 7 are reported herewith. The tabulation indicates the use of phenylhydrazin and the ultimate result in the remaining 21 cases.

TABLE 1.

Case.	Age, years, sex.	Comment.
1–4	..	Reported. Excellent control or complete remission.
5	31 F.	Excellent control on 1.3 to 1.6 gm. twice a year. Phenylhydrazin not necessary for the last 1½ years. Total duration 13 years. Patient under treatment 6½ years.
6	55 M.	Excellent control on gradual reduction of dosage from 0.9 gm. each month to 0.9 gm., every 3 months. Normal erythrocyte count last 6 months without phenylhydrazin. Total duration 12 years. Patient under treatment 6 years.
7	55 M.	Excellent control with normal blood count on 0.1 gm. each week. No evidence of renal insufficiency after 5 years of treatment. Slight increase of retention of dye on test of hepatic function after 12 years of splenomegaly and 5 years of treatment. Total duration of disease 13 years. Patient under treatment 6 years.
8	62 M.	Good control on 0.2 gm. weekly. Accidental death 1½ years later. Total duration, 4+ years.
9	56 M.	Fairly good control with 0.2 gm. daily for 5 days each month. Cardiac (?) death 3½ years later. Total duration, 12 years.
10	59 M.	Good control 1½ years later on 0.1 gm. 3 times a week. Drug discontinued because of cerebral thrombosis. Venesections since then. Living in poor health 4½ years later. Total duration, 8 years.
11	25 M.	Good control 4 years later on 0.2 gm. weekly. Treated by various other methods.
12	64 M.	Fairly good control 3 years later. Four courses with total dosage of 4 gm. in each course. Amputation of leg for arteriosclerotic disease.
13	55 M.	Fairly good control 3 years later. Inadequate treatment. Prostatectomy.

TABLE 1.—(*Continued.*)

Case	Age, years, sex.	Comment.
14	62 F.	Inadequate treatment. Death 3 (?) years later.
15	43 M.	Inadequate treatment. Treated by various methods. Death 6 years later. Total duration, 10 years.
16	58 M.	Inadequate treatment. Two courses only. Death 4 years later. Total duration 12 years.
17	56 M.	Inadequate treatment. Death 6 months later. Cause indeterminate.
18	65 M.	Data inadequate. Living 4 years later.
19	67 M.	Drug discontinued because of age and superficial thrombosis. Death 1 year later. Cardiac (?).
20	63 F.	Drug discontinued. Total dosage only 2.6 gm. Death 6 months later; cerebral hemorrhage.
21	56 M.	Drug discontinued. Took only 0.7 gm. Indications of frontal lobe tumor. Death 1 year later.
22	52 F.	Drug discontinued because of nausea and vomiting. Living 5 years later. Immature leukocytes, 5.5 per cent.
23	43 M.	Hypernephroma and polycythemia vera. Initial course of treatment. Venesections later. Recurrence of hypernephroma 4 years later.
24	62 F.	Death under initial course of treatment. Total 4 gm. Severe phlebitis. Total duration 7 years. Case reported elsewhere.[9]
25	66 F.	Carcinoma of the breast and polycythemia vera. Short preoperative course only of phenylhydrazin. Death following operation. Case reported elsewhere.[9]

In 9 of these 21 tabulated cases, on which data are less complete, fairly good or good control of the disease was secured. Hence, in 13 of the 25 cases it would seem that treatment resulted in definite improvement. In 4 cases inadequate treatment was given; these are not included in our study. One case of carcinoma of the breast, 1 of hypernephroma, and 1 of tumor of the frontal lobe can also be discarded from consideration. In 3 cases the drug was discontinued because of the age and general condition of the patient; it had not yet been learned that patients aged more than 60 years, with advanced arteriosclerosis and visceral disease, are likely to react quickly and seriously to phenylhydrazin. Eliminating these 10 cases, thus reducing the number from 25 to 15, in 13 of 15 cases fairly good, good or excellent results were obtained with phenylhydrazin. There was 1 death under treatment; the patient was aged 62 years and had portal thrombophlebitis. This and other fatal cases have been reported by Giffin and Conner. In 1 case, data are entirely inadequate.

Of the 25 patients, 12 died within a period of 6 years; however, eliminating cases of carcinoma of the breast, hypernephroma, cerebral tumor, and 1 accidental death, the number of deaths is 8. Four of these patients were aged more than 60 years when they came under our observation. Only 1 patient aged less than 60 years, who was given adequate treatment had died of the disease; this patient had been ill for at least 12 years.

Of the entire group of 37 patients, 12 were not treated under our immediate observation. The following tabulation indicates the ultimate outcome and treatment in this group:

TABLE 2.—CASES NOT UNDER IMMEDIATE OBSERVATION.

Case.	Age, years, and sex.	Comment.
26	35 F.	Phenylhydrazin. Excellent control followed by complete remission. Treated at home.
27	36 F.	Phenylhydrazin at home with fair control. Splenectomy later. Living 2½ years after operation.
28	38 M.	Phenylhydrazin. Inadequate treatment at home. Fair control. Good health 5 years later.
29	62 M.	Phenylhydrazin at home with relief of symptoms. Death 2 years later from pneumonia.
30	38 F.	Radium treatment; splenectomy. Death following operation. Immature cells in blood.
31	69 F.	Treated by venesection. Fairly good health 5 years later.
32	58 M.	Death 8 months later; cause indeterminate.
33	57 M.	Surgical case; no record of treatment.
34	59 M.	No record of treatment; not traced.
35	58 F.	Inoperable hypernephroma and polycythemia; not traced.
36	54 M.	Treated at home; not traced.
37	45 F.	Treated at home; not traced.

Only 4 of 8 patients treated at home, to our knowledge, were given phenylhydrazin. Excellent control followed by complete remission for 2 years without administration of the drug was reported in 1 of these 4 cases. The patient was a woman, aged 35 years, who came under our observation August 20, 1926. For 2 years after the initial course of treatment the polycythemic state recurred at intervals, but was easily controlled by a short course of the drug. There was no evidence of increased tolerance. A report dated April 15, 1931, stated that the patient had not taken phenylhydrazin for 2 years and the blood count had remained within normal limits. She was working regularly as a teacher and did not complain of symptoms which could be attributed to polycythemia vera. The condition of the other 3 patients was fairly well controlled, but the treatment was apparently inadequate.

Data on Cases Under Observation from 1912 to 1919. Usually it is stated in the literature that death occurs in cases of polycythemia vera within 6 or 8 years. It is very difficult in a disease of this character, in which the history of onset frequently is indefinite, to determine the exact duration of the disease. In order to obtain a more definite idea of prognosis we have reviewed the cases of polycythemia vera observed at The Mayo Clinic between the years 1912 and 1919 inclusive. In 14 cases the diagnosis was definite.

We have obtained information concerning 12 of these. Death occurred shortly after decompression for increased intracranial pressure in 1 of the 12. Necropsy disclosed enlargement of the pituitary gland which was due to distention of the vascular channels. Of the 11 remaining patients, 9 died subsequently. Two were living at the time of the last report, 10 and 13 years, respectively, after they had been first examined, the total duration of disease having been 15 and 13 years, respectively. The average length of the disease of the 9 patients who died was 10 years; this average would be slightly increased by the elimination of 1 patient who had been ill for only 3 years. The records of these patients seem to show that probably the onset of the disease in every instance was somewhat earlier than was indicated, so that a total duration of 10 years undoubtedly is a conservative estimate. It can be stated, therefore, that this small group of cases indicates a longer duration of disease than that which usually is reported in the literature. In this period the patients were treated by means of radium, Roentgen rays, and venesection. The records were also reviewed for evidence of cyclic phenomena; fluctuations in the degree of erythrocytosis occurred, but whether there had been actual remissions in the course of the disease could not be determined. However, there were no positive data in the records to indicate complete remissions accompanied by normal health, and one would infer that the prolonged remissions observed following the administration of phenylhydrazin are not a natural feature of the disease.

The Toxicity of Phenylhydrazin Hydrochlorid. There has been a great deal of discussion in the literature concerning the toxic effect of phenylhydrazin hydrochlorid on the liver and kidneys. Many drugs, however, are harmful in large dosage and therefore a consideration of dosage is of special importance. Stealy[15] reported a case of polycythemia vera in which treatment with phenylhydrazin had been given for 3 years; during this time there was no clinical or laboratory evidence of deranged hepatic or renal function.* In 3 of our cases, blood urea estimations and urinalysis were normal after 5 years, 1 year, and 1 year, respectively, of initial treatment. In 1 case the dye test for hepatic function was normal after 1 year of active treatment. In 1 case retention of dye was graded 1, 5 years after the institution of treatment of a man, aged 64 years, with a total duration of disease of at least 12 years. Allen and Giffin have shown that dogs receiving 1.26 gm. of phenylhydrazin for each kg. of body weight in 146 divided doses over a period of 8 months, did not excrete abnormal urine, and had normal blood urea and normal excretion of phenolsulphonephthalein at the end of that period; significant retention of the dye on test for hepatic function

* In a paper published after completion of this article, Stealy records his observations on this case over a period of 7¼ years; there was no evidence of damage to hepatic or renal function (Polycythemia Vera. J. Am. Med. Assn., 1932, **98**, 1714).

was not apparent. Allen and Barker studied the organs of 2 of the 3 animals used in these experiments; they found that the livers of these animals were essentially normal and that there was no abnormality of the kidneys which could be attributed to phenylhydrazin. They also found that the kidneys and livers of animals given an amount of phenylhydrazin daily sufficient to cause death on the 5th day, manifested only atrophy of the parenchymal cells of the liver and overloading of the convoluted tubules of the kidneys with iron. It seems to be conclusive that the relatively small dosage necessary for the control of polycythemia vera in man is not harmful to renal and hepatic function in the absence of advanced visceral or vascular disease. Moreover, in our experience examination of the blood films morphologically during treatment has not revealed marked toxic abnormalities of leukocytes. However, it is most important to recognize that clinical experience has shown that phenylhydrazin in small dosage may cause rapid hemolysis and fatal outcome among older patients with advanced visceral disease. Whether this is due entirely to hemolysis with its sudden temporary increase in the nitrogenous products of the blood, or partly also to some special toxicity, has not been determined. This aspect of treatment has been considered by Giffin and Conner.

Tolerance to Phenylhydrazin Hydrochlorid. Our experience with the administration of phenylhydrazin hydrochlorid to human beings does not indicate that an abnormal tolerance to the drug develops. In every instance when the erythrocyte count has become abnormally high after treatment with phenylhydrazin, readministration of the drug was followed by satisfactory reduction of erythrocytes. It is true that after the production of anemia with phenylhydrazin the administration of more of the drug does not decrease the erythrocytes proportionately, but the conclusion concerning tolerance should be based either on a normal or increased number of erythrocytes. Bratley, *et al.*,[4] have recently concluded that anemic rabbits and dogs acquire tolerance to the drug; but it appears that they have not taken into account the significance of the low erythrocyte level at the beginning of their experiments. The chief requirement for experimental work bearing on the question of clinical tolerance is that the erythrocytes should be at the same or similar levels in all experiments. It would be expected that more of the drug would be necessary to reduce the erythrocytes from 3,000,000 to 2,000,000, than from 5,000,000 to 4,000,000, but this would not be regarded as evidence in favor of increased tolerance because regeneration is more active when the count is low. Experiments of the authors indicated that if an animal is given daily 12 mg. of the drug for each kg. of body weight, the number of erythrocytes drops approximately 1,500,000 cells and then maintains a level on continuance of the same dosage. This does not indicate increased tolerance but more active regeneration; however, if the number of erythrocytes is

allowed to return to normal the same amount of the drug will have the same effect on the number of erythrocytes.

Miscellaneous Considerations. In 2 cases of the series of 37, immature cells of the granular series appeared in the blood in appreciable numbers, presenting a morphologic picture similar to that of chronic myelogenous leukemia. In 1 of these cases phenylhydrazin had not been given; in the other, the drug was discontinued because it produced nausea and vomiting. In both of these cases immature cells appeared late in the course of the disease and constituted only 5 or 6 per cent of the leukocytes. In none of the cases in which phenylhydrazin was used, even in larger amounts and over prolonged periods, did immature cells appear, although marked leukocytosis was common. Myelocytes were sometimes present at the time of first examination, but these disappeared following treatment.

It should be assumed that polycythemia vera will result fatally usually within 10 or 15 years from the time of onset. Treatment may logically be directed to maintenance of reduced blood volume on the theory that this may delay the advancement of vascular and visceral disease. Phenylhydrazin will safely reduce the blood volume if patients are not too old or in a too advanced stage of the disease, but should be administered with great caution or not at all to old, or debilitated patients. During the initial course of treatment the patients are best treated in hospital on an ambulatory regimen in order to keep the circulation free and decrease the likelihood of venous thrombosis. An initial hemolysis can usually be produced by the administration of 0.1 gm. of phenylhydrazin 2 or 3 times a day until a total of from 3 to 4 gm. has been given. Occasionally resistant cases will be found which require a larger total dosage. In these cases it has been our practice to discontinue the drug after 3 gm. has been given because of the cumulative effect, and if necessary to resume treatment in a few days giving additional total dosage of 1 gm. in each subsequent series, repeating this procedure until a proper degree of hemolysis has been obtained. An active preparation of phenylhydrazin must be obtained and it should be freshly placed in capsules each week as needed.

After the initial course of treatment, and within a few weeks at most, phenylhydrazin should be given in 0.1-gm. doses 3 or 4 times a week or in sufficient dosage to maintain the erythrocyte level between 5 and 6 millions. Our patients are now instructed to take from 0.2 to 0.4 gm. each Wednesday and to have the erythrocytes counted regularly, at least once a month. They are warned against increasing or decreasing the dosage too much or withdrawing the drug without careful consideration; these instructions prevent extreme swings in erythrocyte count and blood volume. Complete remissions have occurred on this regimen, but cases have not been observed long enough to decide whether life will be prolonged.

Summary. The experience with 37 patients with polycythemia vera, who were observed from 4 to 6 years, shows conclusively that after the initial course of phenylhydrazin has been satisfactorily completed, the disease frequently can be controlled by the administration of a very small dose (0.1 to 0.4 gm.) of the drug each week. This control in some instances has been accomplished by a dosage which has been shown to be ineffective experimentally so far as hemolysis is concerned (for example, 0.06 gm. a month); this fact leads one to suspect that phenylhydrazin may have another effect on the blood picture such as an inhibitory effect on the production of erythrocytes, although it is fairly well proved to have a stimulating effect on the production of leukocytes. This suspicion cannot at present be proved but is worthy of further consideration. Some of the patients after from 2 or 4 years of treatment have been able to dispense with the drug entirely and maintain a normal number of erythrocytes. Other patients have found it necessary to use the drug regularly; in some instances subsequent courses of daily dosage have been necessary. The occurrence of complete remission in some of the cases is apparently of especial significance. The untoward effects of phenylhydrazin are also considered; this phase of the subject has been amplified in a paper by Giffin and Conner. Phenylhydrazin should not be given if the diagnosis of polycythemia vera, with increased blood volume, cannot be well established (see McNamara and Sansum[13]).

NOTE.—Cases 1, 8, 12, 13, 15, 16 and 17 of this study are cases 4, 1, 5, 6, 3, 7 and 2, respectively, of the report of Brown and Giffin.[5] Case 7 of this study is the case reported by Allen.[1] Cases 24 and 25 of this study are cases 3 and 4, respectively, in the report of Giffin and Conner.[10]

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A DISCUSSION OF THE RÔLE OF ARTERIAL THROMBOSIS IN THE VISCERAL DISEASES OF MIDDLE LIFE, BASED UPON ANALOGIES DRAWN FROM CORONARY THROMBOSIS.*

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The views of the writer would perhaps be more accurately indicated if the title of the paper had been phrased in interrogatory form, for it is his purpose in discussing the subject rather to inquire what may be the part played by arterial thrombosis in the viscera than to affirm what that rôle is. Only in the case of the heart and the brain have we anything approaching satisfactory information concerning the incidence and significance of arterial thrombosis. With respect to the other organs (pancreas, spleen, kidneys, intestines, liver, lungs) our knowledge is surprisingly scanty, concerning both the pathologic and the clinical aspects of such thrombosis. For this reason much of the discussion which follows must unfortunately be hypothetical in character and based upon analogies rather than on actual observations. But that arterial thrombosis plays a rôle of some importance in the diseases of viscera other than the heart and brain, and that the subject has hitherto received surprisingly little attention, cannot be doubted.

The steady growth in our knowledge concerning disease of the coronary arteries has established a number of important facts which it is desirable to review because of the bearing they may have upon disease of the arteries in other viscera: (1) The great frequency of coronary arteriosclerosis in the middle and later years of life; (2) the lack of any close relationship between coronary and peripheral arteriosclerosis; (3) the surprisingly early age at which coronary artery disease often manifests itself; (4) the frequent existence of coronary disease without preëxisting arterial hypertension; (5) the

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importance and frequency of thrombosis in the course of coronary arteriosclerosis.

Evidence as to the validity of the above statements may be summarized as follows: The great frequency of coronary arteriosclerosis in the middle years of life is shown both by every-day clinical experience and by postmortem findings. In persons of over 40 years of age heart disease is much the greatest single cause of death, and among the causes of heart disease in such persons coronary artery disease easily stands first.

The conception of arteriosclerosis as a "general" process has been so widely accepted that we have almost lost sight of the fact that the process is notoriously irregular in its distribution and that there is little or no relationship between the state of the arteries in the heart or the other viscera and that of the peripheral arteries. The relative independence of visceral and peripheral arteriosclerosis has been emphasized by Fitz,[1] by Romberg[2] and by many others.

Recent statistics concerning coronary artery disease have made it clear that such disease is very common in early middle life. In an analysis of 287 cases of coronary thrombosis (Conner and Holt[3]) it was shown that in 75 per cent of the patients the symptoms appeared before the age of 61 years and in 33 per cent before the age of 51 years. In this connection it is well to recall that Romberg[2] many years ago insisted that we must regard arteriosclerosis, not as a disease of old age ("Alterskrankheit"), but rather as a process of wearing out ("Abnutzungskrankheit"), and that this wearing-out process may begin very much earlier in certain structures or organs than in others.

The frequent occurrence of coronary thrombosis without preexisting hypertension has been clearly shown by the figures of Parkinson and Bedford,[4] Levine,[5] and Conner and Holt;[3] and it seems safe to say that at the most not more than half of the cases of coronary artery disease are associated with arterial hypertension. In their recent study of 500 cases of angina pectoris White and Bland[6] found that only in 36 per cent of the cases was there an associated arterial hypertension.

As to the importance and frequency of the complication of thrombosis in coronary arteriosclerosis there can be no question, although accurate statistical figures are not available. Not only does thrombosis supervene in a large proportion of the cases of angina pectoris, but even more frequently do the symptoms of the attack of coronary closure give the first and only intimation that serious coronary disease exists. We have learned during recent years that most attacks of coronary thrombosis are not immediately fatal and that the occurrence of 2 or more such attacks in the same individual is the rule rather than the exception.

Relation of Arterial Thrombosis to Arteriosclerosis. With the growing appreciation of the vast clinical importance of coronary throm-

bosis the question is being asked more and more whether the atherosclerotic changes in the vessel wall are the chief causal factor or whether there are other factors, such as changes in the character of the blood itself, which play an important rôle. Unfortunately the question cannot be answered at present. There are various reasons for thinking that other factors may play a part in the production of thrombosis, but upon the evidence at present available we are forced to believe that atherosclerotic changes in the arterial wall are an essential, and probably are the chief, prerequisite for the formation of the thrombus.

Having discussed the more important facts concerning disease of the arteries of the heart, the question arises as to how far these facts can be applied to the arteries of other viscera. Is there evidence to show that arteriosclerosis is common in the other viscera in the middle years of life, and if so, is thrombosis the frequent result of such sclerosis that we know it to be in the case of the coronary arteries?

All the evidence at hand indicates that the tendency to atherosclerotic change, which is so marked a feature in the heart in middle life, is shared by most of the other viscera. We know that such changes are very common in the kidneys, in the brain, in branches of the mesenteric arteries. We know that they are not infrequent in the arteries of the pancreas and the spleen and, under certain special conditions, even in the branches of the pulmonary arteries; but we know very little concerning the occurrence of *thrombosis* in the diseased arteries of most of these viscera. Only in the case of the brain is the clinical diagnosis of arterial thrombosis made with any frequency, and even with this organ there is often a hesitancy about making the diagnosis if the patient be one in early middle life. Yet if sclerosis be at all common in the arteries of the various viscera, it is hard to believe that thrombosis is not a frequent complication of such arteriosclerosis.

The question of thrombosis is, we know, closely linked with that of *infarction*, for it is infarction which gives rise to most of the symptoms resulting from thrombosis. Indeed without some infarction it is doubtful if the clinical diagnosis of thrombosis is ever possible. Whether or not infarction results is determined chiefly by the character of the arterial branching and the scarcity or abundance of anastomoses; but in the case of most of the viscera infarction is known to occur from arterial closure due to embolism.

So while, as has been said, we know comparatively little about the actual occurrence of thrombosis, with or without infarction, in the viscera other than the heart and brain, it is difficult to believe that arteriosclerosis, which is known to be common in the other viscera, can proceed without the frequent occurrence of thrombosis. Moreover, in kidneys which are the seat of arteriosclerotic changes it is a common experience to see one or more depressed surface

scars which can best be explained on the basis of an infarct from an old thrombotic closure; one occasionally sees similar depressed scars on the surface of the spleen without anything in the patient's history to suggest that such an old infarct has had an embolic origin.

If, however, the analogy between the heart and the other viscera hold, and if thrombosis in disease of the arteries of these viscera be of frequent occurrence, why is it that the diagnosis of such thrombosis is rarely or never made, whereas the diagnosis of coronary thrombosis is made so frequently and so easily?

The answer lies in part, no doubt, in the special characteristics of the heart itself which favor the making of such a diagnosis. Thrombosis of a coronary artery frequently leads to early death and to the prompt confirmation of the diagnosis. The peculiar features of the pain and certain other symptoms are much more pathognomonic than in the case of other viscera, the electrocardiogram is usually characteristic, and the heart is so accessible to physical examination that the physical signs are often helpful; whereas in the case of the other organs the conditions for diagnosis are much less favorable. Since the cases are probably rarely fatal, confirmation of the diagnosis by autopsy will be lacking, and, in the case of the abdominal viscera, the pain and the disturbances of function are likely to be much less characteristic and helpful. Moreover, most of the other organs are much more liable to other acute diseases which may simulate infarction and confuse the diagnosis.

But that is not the whole answer. One reason for our failure to recognize thrombosis in the arteries of the other viscera lies, I think, in the fact that we fail to have the possibility in mind and so have failed to develop diagnostic criteria.

Is it beyond reasonable hope that such criteria may be developed? I believe not. Twenty years ago coronary thrombosis was hardly more than a pathological curiosity. Repeatedly in the older literature one finds statements indicating that its clinical diagnosis can hardly be expected. In the writings of two recent great clinicians, Osler and Mackenzie, a clear understanding of the clinical picture of this condition is entirely lacking, whereas now there is hardly a disease in the whole realm of internal medicine which can be recognized so promptly and so certainly. With the development of its diagnostic signs we have in turn come to know much more concerning its natural history and have learned to recognize its milder and more benign aspects. May we not expect, after what has happened in the case of coronary thrombosis, that when we begin to look for the signs of thrombosis in the arteries of the kidneys, the spleen, the pancreas and the mesentery, we shall gradually develop criteria which will ultimately make such diagnoses possible?

Let us now consider in how far it may be possible to construct a framework of diagnosis for thrombosis of the arteries of these viscera. For this purpose we have material from two different sources: (1) The symptoms known to result from thrombosis and infarction in the heart; (2) those which result from the infarction which follows the lodgment of emboli in various organs. Thus infarction in the kidneys, spleen, brain and lungs is frequently recognizable, and that in the gastrointestinal tract occasionally so. But the diagnosis is rarely made unless there is reasonably certain knowledge of the existence of conditions which would provide a source for such emboli. In the case of such organs as the pancreas, the liver, the thyroid gland and the uterus we are without this aid from embolic infarction.

In attempting to construct theoretically a framework of diagnostic symptoms for arterial thrombosis in other viscera from analogy with the symptoms of coronary thrombosis, there are two which seem applicable to any organ in which thrombosis is accompanied by infarction. These are *fever* and *leukocytosis*. Both of these are presumably the result of the reactive inflammation excited by the presence of the infarct, and it seems reasonable to expect that they would be present in the case of infarction in any other organ. The other general symptoms, such as shock, pallor, sweating, vomiting and a fall in blood pressure, we might expect to be less pronounced and striking in the case of other viscera than in thrombosis and infarction in the heart. In regard to other symptoms, such as pain and disturbances of function, these would, of course, vary with the individual organs involved. It seems probable that the time relationship between the onset of pain and that of fever may have some diagnostic significance, since the pain should *precede* the fever by an interval of at least some hours.

Let us turn now to a brief consideration of the probable diagnostic features of arterial thrombosis in the several organs.

Kidney. We know fairly well what might be expected in the way of symptoms of thrombosis in the kidney from those which arise as the result of embolic infarction in that organ, and it is very surprising, in view of the frequency with which evidences of old infarcts are seen in arteriosclerotic kidneys, that the clinical diagnosis of arterial thrombosis should be rarely, if ever, made. This must be chiefly because the possibility of such thrombosis is not held in mind. In a person of arteriosclerotic age in whom there is no ground for expecting the discharge of arterial emboli, the occurrence of dull pain and tenderness in the flank, of more or less fever and leukocytosis, and of red cells and albumin in the urine (if absent previously) would seem to justify such a diagnosis.

Spleen. Postmortem evidences of old healed infarcts in the spleens of persons who show no source for arterial emboli suggest that such infarcts are the result of arterial thrombosis. The

symptoms of embolic infarction of this organ are usually so distinct that infarction due to thrombosis should be recognizable if only its possibility were kept in mind. Pain of the pleural type, fever, leukocytosis, tenderness and perhaps muscular rigidity in the splenic region, and not infrequently a to-and-fro perisplenitic friction sound over some part of the splenic area, make a sufficiently distinctive picture to warrant the diagnosis of arterial thrombosis, if there is nothing to justify the suspicion of embolic infarction and if other satisfactory explanations of the symptoms are lacking. Thrombotic infarction seems especially prone to occur in spleens which are the seat of massive enlargement, of whatever nature, and in the presence of splenomegaly the possibility of such infarction should be constantly remembered.

Pancreas. Very little is known concerning either arterial thrombosis or arterial embolism in the pancreas. A search of both the pathologic and the clinical literature has yielded surprisingly little information upon this subject. The arteries of the pancreas are frequently the seat of arteriosclerosis.* Most of the arterial branches to the pancreas arise from the splenic artery, which is notoriously prone to extensive arteriosclerotic change, and there seems every reason to expect that the sharply angled branches supplying the pancreas should sometimes be the seat of thrombosis. If thrombosis and infarction occur, nothing is known as to their clinical features. One would expect to find pain of greater or less severity in the epigastric or umbilical regions, with perhaps some tenderness, some degree of shock, some fever and leukocytosis and probably nausea and vomiting—all symptoms which, it must be confessed, might well be evoked by disturbances in various other organs in that neighborhood. If, however, in a person of appropriate age there were the simultaneous appearance of sugar in the urine, that fact would go far toward justifying the diagnosis of arterial thrombosis. For a long time it has seemed to me that some of the abruptly appearing glycosurias in arteriosclerotic subjects might well be the result of pancreatic thrombosis and infarction.

The Mesentery. Infarctions of the gastrointestinal tract are not rare, and the more massive forms are sometimes recognized clinically, although much more often the diagnosis is made first at operation or at the autopsy table. In the large series of cases analyzed by Trotter,[8] a clinical diagnosis was rare. As infarction may result from arterial embolism and from thrombosis of the mesenteric veins as well as from arterial thrombosis, even when the diagnosis of mesenteric infarction seems justified, it is difficult to be sure that the cause of the infarction is arterial thrombosis.

That arteriosclerosis is common in the mesenteric arteries is

* In Brooks' study[7] of visceral arteriosclerosis the pancreas is listed as fourth in the order of frequency of arterial disease, following the heart, brain and kidneys.

thoroughly established (Ortner,[9] Zesas,[10] Sauvé,[11] Lagane[12]), and there seems reason to believe that thrombosis, especially of the smaller arterial branches, is of much more frequent occurrence than is its clinical recognition. In this connection Trotter[8] comments as follows: "Two circumstances have been responsible for the failure in recognition of the disease; in the first place the clinical picture is extremely variable and in most cases very incomplete, and in the second place the condition has been regarded as so uncommon that it has frequently not even been considered."

As is the case in most other organs, closure of a mesenteric artery or one of its branches does not always result in infarction, and in the absence of infarction we can hardly expect that the arterial thrombosis will be manifest clinically.* Whether or not infarction occurs depends upon several factors: the size of the arterial branch occluded, the state of the venous circulation, the degree of distention or emptiness of the gut, and perhaps individual variations in the arterial anastomoses. It is well known that infarction occurs very much more frequently in the area of gut supplied by the superior mesenteric artery than in that supplied by the inferior.

It is to be expected that the symptoms of intestinal infarction, from whatever cause, would show great variations in character and severity, depending upon the size and the location of the area of gut involved. The clinical picture is usually divided into two stages, with at first symptoms due to irritation of the gut and later with those due to paralysis. At the onset there is violent crampy pain, nausea and vomiting, sometimes diarrhea, and usually prostration, collapse and sweating. The vomitus is often blood-stained, and the stools frequently contain blood. After a day or two, and often after a temporary cessation of the severe pain, the symptoms of paralytic ileus appear—with complete obstipation, great distention, persistent vomiting, pain and tenderness. Among the recorded cases the temperature has been variable, usually elevated, but sometimes normal or subnormal. It seems probable, however, that some degree of fever and leukocytosis must be present in every case at some stage.

Even if the diagnosis of intestinal infarction seems justified, there is still the problem of distinguishing between the three possible sets of causes—mesenteric venous thrombosis, arterial embolism and arterial thrombosis. If, however, it is possible to exclude the usual sources of an arterial embolus and such conditions in the abdomen as predispose to thrombosis in the branches of the portal vein (appendicitis and other severe intestinal inflammations, hepatic cirrhosis, thrombosis of portal veins, etc.) and if the patient be one

* In Trotter's large compilation[8] thrombosis of the superior mesenteric artery is believed to have occurred in 61 cases. Among these hemorrhagic infarction was found in 34, hemorrhages or intense engorgement in 12, mucous catarrh in 1 and no changes in the intestines in 3. In the remaining 11 cases the patient either recovered or died without autopsy.

in middle life there would be a strong presumption that the infarction was the result of arterial thrombosis.

The recognition of thrombosis of branches of the hepatic artery in the liver and of the bronchial arteries in the lungs is made extremely difficult by the fact that in each of these organs the double vascular supply so reduces the likelihood of infarction from such thrombosis that its occurrence is almost unknown. The same is true of the two centrally placed organs, the thyroid gland and the uterus, which have an arterial supply from each side of the body. In the case of large fibromyomata of the uterus, however, arterial thrombosis is known to occur and to result in areas of necrosis and softening which may give rise to severe symptoms.

It is recognized, of course, that such a theoretical discussion of the diagnosis of arterial thrombosis and infarction in the abdominal organs may prove to be in certain respects quite inaccurate, and these suggestions are offered merely in the hope that they will serve to direct attention to a subject which must have some clinical significance and which hitherto has been given little consideration. Everyone knows how common it is to encounter obscure, acute illnesses marked by more or less abdominal pain, fever and prostration, in which no diagnosis can be ventured. Some of these may well belong to the group under consideration. One of the chief difficulties in the working out of such a clinical picture is the fact that only rarely will it be possible to get prompt postmortem information in suspected cases, as such attacks in the abdominal viscera must usually result in recovery. If we are ever to gain further knowledge, this must come from the combined efforts of the clinician and the pathologist. At the present time the pathologist is as lax in searching for arterial lesions in the abdominal viscera as is the internist in seeking for their signs during life. The publication of the clinical reports of even a very few cases of arterial thrombosis in the spleen, pancreas, or kidneys with postmortem confirmation would inevitably excite interest in the subject and would result, I believe, in the steady accumulation of facts which ultimately would place the clinical diagnosis of such lesions upon a firm basis.

Summary. Attention is called to the fact that whereas thrombosis in the arteries of the heart and of the brain is known to be common and is easy of clinical recognition, almost nothing is known concerning the symptoms of arterial thrombosis in the abdominal viscera. Nevertheless the frequent occurrence of degenerative changes in the arteries of the pancreas, kidneys, spleen and mesentery indicate that thrombosis in these vessels cannot be rare.

The failure to recognize attacks of arterial thrombosis in the abdominal organs must be due in part to the inherent difficulties of diagnosis, but is almost certainly also due partly to our failure to have the possibility of such attacks in mind and to have accumulated pertinent evidence.

An attempt is made to construct a framework of diagnosis for arterial thrombosis in the kidney, pancreas, spleen and mesentery by utilizing certain symptoms associated with thrombotic infarction in the heart (fever, leukocytosis) and those which result from infarction due to embolism in the kidney, spleen and mesentery.

It seems probable that when both internists and pathologists begin seriously to seek for evidences of such thromboses and to correlate their findings, the difficulties of diagnosis will be found to be not insurmountable, and the lineaments of the respective clinical pictures will gradually emerge from the present obscurity, much as have those of the diagnosis of coronary thrombosis.

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FAMILIAL EOSINOPHILIA.

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This report details the study of four families in each of which several members exhibited a distinct, persisting and unexplained eosinophilia. The term familial is used to indicate the presence of eosinophilia in several members of a family, in whom none of the known causes of eosinophilia could be found, such as allergic states, dermatoses and parasitic infestations, especially trichinosis. A few authors have used the designation "constitutional eosinophilia"

to refer to this condition, whether familial or in but one member of a family.

The terms constitutional eosinophilia and familial eosinophilia seem to have been used synonymously. The latter, however, has been adopted for use here as being more descriptive and having been the first in use.

In spite of the fact that as early as 1911 Klinkert[1] called attention to familial eosinophilia, its importance seems to have been neglected. So few examples can be found in the literature that one can only guess as to its frequency. Klinkert's report described a family of 6 with eosinophil counts varying from 7 to 15 per cent. However, in this family there seemed to be an adequate explanation of the eosinophilia, for 3 of 5 children exhibited allergic manifestations in the form of asthma, angioneurotic edema and urticaria. I have previously noted eosinophilia in 3 generations of the family of a patient with eosinophilic leukocytosis and Hodgkin's disease.[2] Allergic factors were present in all 3 generations.

The family incidence of allergy and of transmissible parasitic disease doubtless accounts for some of the eosinophilias that have been classified as familial or constitutional. Under the title of familial eosinophilia in this paper, however, are grouped only those families in which all of the usually accepted causes of eosinophilia have been excluded, according to our present methods of investigation. In the remaining literature cited, the possibility of allergic eosinophilia and its other causes have been excluded. Such a family was reported by Gaugain,[3] in which the mother had an eosinophilia of 19 per cent, and 3 children, 10, 14 and 15 per cent, respectively. The most completely studied example of familial eosinophilia was published by Armand-Delille, Hurst and Sorapure.[4] The patient, a boy aged 8 years, had an eosinophilia of between 51 and 62 per cent. Three sisters and a brother had eosinophil counts of 14, 21, 27 and 27 per cent, respectively, and the father, 7 per cent. All of the usual causes of eosinophilia were carefully excluded. Similar instances under the designation of constitutional eosinophilia are reported by Bastai,[5] Cirio,[6] Spiro and Pfanner,[7] Smits,[8] Lucas[9] and Cattaneo.[10] Fanton[11] spoke of "so-called eosinophil diathesis" in recording eosinophilia in a father and daughter with no allergic history.

In Chart I are summarized the eosinophil percentages in 6 families reported in the medical literature.

The opportunity to investigate 4 families with eosinophilia has been afforded during the past year. In each instance the patient, through whom attention was attracted to the family, had been on the Medical Service of Dr. Stengel in this hospital.

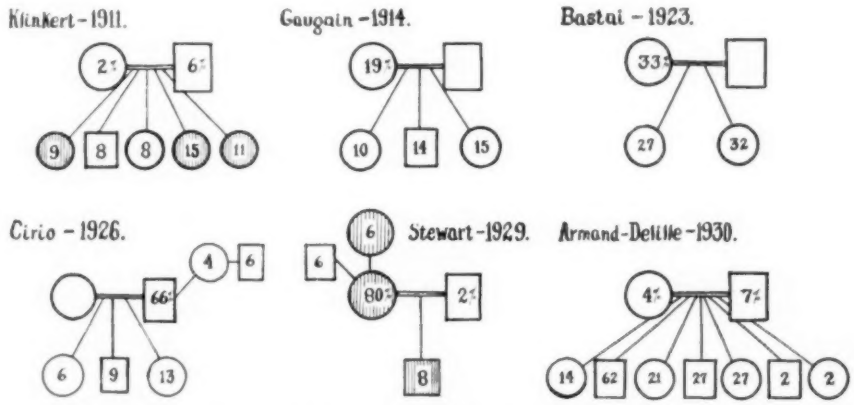
Report of Cases. CASE 1.—E. P., a girl, aged 18 years, was admitted on November 24, 1930, because of severe cough. For 2 years there had been symptoms suggesting pulmonary infection—increasing cough, dysp-

nea, purulent sputa, chest pains, irregular fever and loss of weight. At times there were severe attacks of diarrhea and generalized abdominal pain.

Physical Examination. The patient was greatly emaciated. Examination of the chest, which was of a phthisic configuration, revealed signs of extensive infiltration of the lungs with cavities at both apices. Tenderness was complained of over the colon, and a mass could be palpated in the region of the cecum. There was no enlargement of the spleen or lymph nodes.

Laboratory Data. The red blood count showed a moderate secondary anemia, averaging 4,200,000 cells, with a hemoglobin content of 60 per cent (Sahli). The leukocyte count remained elevated, at a fairly constant level of 20,000 cells, with a persistent eosinophilia which, at times, reached 32 per cent.

CHART I.—SIX FAMILIES WITH FAMILIAL EOSINOPHILIA.



In this and subsequent charts the presence of allergic manifestations is indicated by cross-hatching. The circles represent females and the squares males. The figures within the circles indicate the percentage of eosinophilia.

The sputum was loaded with tubercle bacilli. Repeated stool examinations were negative for ova and parasites, but contained large numbers of tubercle bacilli. Skin tests, using the usual antigens of inhalants and foods, disclosed no abnormal skin sensitivity. A tuberculin test was not done. Roentgen rays of the chest revealed extensive tuberculosis of both lungs with multiple cavities. No calcifications of cysts of trichinosis were seen in the thoracic musculature.

In brief, the patient suffered from a florid type of pulmonary and probably enteric tuberculosis. There was neither personal nor family history of allergy. The patient stated specifically that she had not been allowed to eat pork in any form for several years, had had no past illness suggestive of trichinosis, and had received no medication which might have induced eosinophilia. There was no history of skin disease.

Comment on Case 1. Tuberculosis was suggested as a possible cause of eosinophilia. It has been reported in infantile tuberculosis by Belloni.[12] Brumlik and Sikl,[13] and Cordier, Croizat and Carle[14] recorded cases of eosinophilia in lymph node tuberculosis, and Grass and Simmert[15] noted eosinophilia as an index of allergy in

tuberculosis. Kilduffe[16] mentioned its occurrence in active tuberculosis. However, when other members of this patient's family were studied, it was found that eosinophilia was present in all of its members, and tuberculosis in none. Therefore this possibility, as the cause of the eosinophilia in this family, seemed improbable. In Chart II are the blood counts made on the patient and her various relatives, as far as the family tree could be traced.

The outstanding features of the data charted are the marked increase in the absolute number of eosinophils in each of the 8 relatives studied and the occurrence of eosinophilia on both the father's and mother's side of the family (the average normal for absolute numbers of eosinophils quoted by Clough[17] is 250 cells per c.mm.). There was no family relationship between the father and mother before marriage. This very unusual finding of eosinophilia in both branches of the family, in the absence of personal and family history of allergy, seemed to cast some doubt on the thought that trichinosis and other parasitic infestations had been excluded. However, in none could a history of trichinosis be obtained. A letter from Dr. J. D. Boger, Health Officer for the City of Lebanon, Pa., where all the family lived, stated that no cases of trichinosis had been seen in that vicinity or reported to the Board of Health during the past 4 years. Stool studies for ova and parasites, which could be done only on the immediate members of the family, were all negative. According to the present clinical methods for determining trichinosis, it was excluded in this family.

Lastly, blood counts were repeated on the immediate family 4 months later, and the absolute numbers of eosinophils coincided closely with the figures recorded in Chart II.

Case 2.—J. L., a boy, aged 12 years, was studied in the Cardiac Section of the Medical Clinic of this hospital on March 7, 1931. He had no special complaints, but was referred by the school physician because he had had "rheumatism" 2 years ago, and rheumatic pains in the left leg 1 year ago. Occasionally he experienced mild precordial pain. There was a history of the usual childhood diseases, including otitis media, but not chorea or scarlet fever. No personal or family history of allergy, skin disease or trichinosis could be elicited.

Physical Examination. The patient was well developed, in a good state of nutrition and had no fever. No evidence of cardiac disease was found, and there was nothing abnormal in the physical examination, except slight pallor of the conjunctivæ and mucous membranes.

Laboratory Data. The erythrocyte count averaged 3,000,000 cells with a hemoglobin content of 60 per cent (Sahli). The leukocyte count was 6000 with 22 per cent eosinophils. No ova or parasites were found in stool examinations. Roentgen rays of the muscles of the shoulder girdle gave no evidence of calcification of trichinal cysts. Here again the persistent eosinophilia seemed an extraneous finding.

Comment on Case 2. It was thought that a low-grade chronic infection, related to the rheumatic pains, and perhaps the moderate secondary anemia, might play a rôle in the causation of the eosino-

CHART II.—EOSINOPHILIA OF FAMILY P.

	Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. P.	Mother	44	85	8,000	57	18	5	20	1600	None.
Mr. P.	Father	50	97	8,500	57	24	2	17	1445	None.
Ed. P.	Daughter	18	55	12,000	60	8	..	32	3840	None.
El. P.	Daughter	12	88	8,400	50	20	2	28	2352	None.
I. P.	Father's bro.	54	87	9,200	62	21	2	15	1380	None.
J. R.	Mother's bro.	55	111	7,500	54	22	2	22	1650	None.
E. F.	Mother's sis.	53	100	7,200	66	18	1	15	1080	None.
E. R.	Mother's bro.	46	92	8,200	72	13	..	15	1230	None.

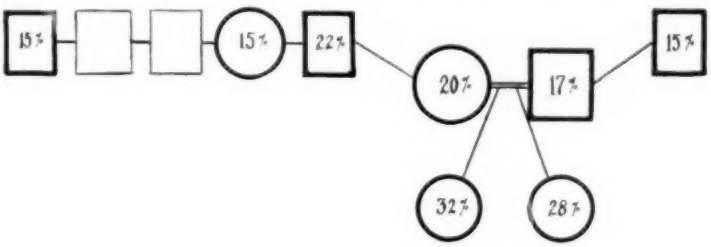
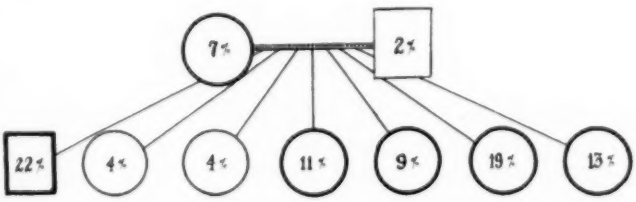


CHART III.—EOSINOPHILIA OF FAMILY L.

	Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. L.	Mother	36	80	8,600	67	25	1	7	602	None.
Mr. L.	Father	39	101	5,000	50	45	3	2	100	None.
J. L.	Son	12	60	6,000	48	28	2	22	1320	None.
A. L.	Daughter	14	83	8,600	59	35	2	4	344	None.
E. L.	Daughter	10	80	8,000	70	26	..	4	320	None.
M. L.	Daughter	8	75	9,000	51	34	4	11	990	None.
R. L.	Daughter	6	69	7,600	52	35	4	9	684	None.
Ja. L.	Daughter	3	61	10,000	56	23	2	19	1900	None.
P. L.	Daughter	3	63	9,000	59	24	4	13	1170	None.



philia. Such a relationship has been described by Akerren,[18] Fiedler[19] and others, and, indeed, several cases of rheumatoid arthritis with myositis and persistent eosinophilia have recently been studied in this hospital. The coincidence of postinfectious anemia with eosinophilia has been noted by Tallqvist[20] and Beifeld and Barnes.[21] Indeed, these explanations were accepted for lack of any better one, until a marked eosinophilia was discovered in other members of this family, whose counts are summarized in Chart III.

Each of the 9 members of the family, except the father, had absolute eosinophil counts above the average normal. All except the patient were quite healthy people, although the 4 sisters had moderate hypochromic anemia. There was no evidence of tuberculosis or chronic infection, and stool studies in each member of the family were negative for ova and parasites. One year later complete blood counts were repeated on every member of the family. The percentages of eosinophilia were essentially unchanged, with the exception of E. L. who previously had 4 per cent (320 eosinophils) and after 1 year had 10 per cent, with a leukocyte count of 8600. The anemia noted in the 4 sisters was not present when the second counts were taken.

Case 3.—T. M., a boy, aged 3 years, was treated in this hospital because of lobar pneumonia. Recovery was uneventful. At the age of 2 years he had been treated here for poor nutrition, secondary anemia and septic tonsils. At that time the blood showed a leukocytosis of from 10 to 18,000 with an eosinophilia reaching as high as 50 per cent. The eosinophilia was present on the second admission, but disappeared completely during the acute stage of pneumonia, to return again to its previous level after convalescence. Otherwise he was an entirely average child in good nutrition and with a slight secondary anemia. There was no personal or family history of allergy, trichinosis or skin disease.

Laboratory Data. Repeated stool studies were negative for ova and parasites. The red blood count averaged 4,300,000 cells, the hemoglobin 75 per cent (Sahli) and the leukocyte count 15,000, with 42 per cent of eosinophils. All other laboratory tests were negative.

Comment on Case 3. Here again, as in Case 2, is represented a patient with chronic infection (septic tonsils), secondary anemia and eosinophilia. The other members of the family exhibiting increased numbers of eosinophils were quite healthy people, but there was found also a slight hypochromic anemia. Examination of the feces gave no evidence of infestation in any member of the family, and all the known factors which might be related to eosinophilia were ruled out.

Case 4.—J. B., a man, aged 38 years, had been admitted several times to the Medical Service of this hospital because of severe asthma of 5 years' duration. Asthma began 2 days after thyroidectomy. It seemed to be of an infectious type, being associated with pansinusitis, but was unrelieved by any medical or surgical procedures. There was no history of allergy in any other member of the family.

Physical Examination. The patient was in a good state of nutrition. Slight cyanosis, polypoid degeneration in the nose with purulent sinus discharge, emphysema and typical lung signs of bronchial asthma were the only positive findings. Between attacks he felt entirely well.

Laboratory Data. Repeated stool examinations were negative for ova and parasites. The red blood count averaged 5,000,000 cells with 95 per cent hemoglobin (Sahli). The leukocyte count remained quite constantly at 12,000 cells, with a persistent eosinophilia as indicated in Chart V.

CHART IV.—EOSINOPHILIA OF FAMILY M.

	Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mr. M.	Father	31	96	7,600	61	33	4	2	152	None.
Mrs. M.	Mother	26	80	6,000	51	39	4	6	360	None.
A. M.	Daughter	5	70	10,000	58	29	3	10	1000	None.
T. M.	Son	3	66	15,000	26	30	2	42	6300	None.
M. M.	Daughter	1	70	10,000	57	29	4	10	1000	None.

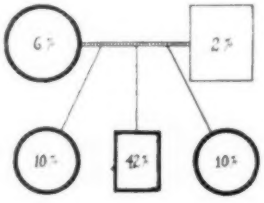
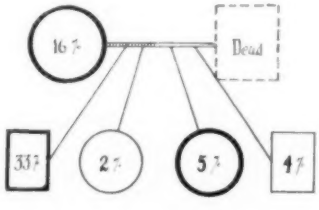


CHART V.—EOSINOPHILIA OF FAMILY B.

	Relation.	Age.	Hgb.	W.b.c.	Neutro.	Lymph.	Mono.	Eos., %	Abs., No.	Allergy.
Mrs. B.	Mother	69	..	8,000	57	24	3	16	1280	None.
J. B.	Son	38	90	10,300	42	20	5	33	3399	Asthma.
E. B.	Son	41	..	8,500	67	22	7	4	340	None.
G. B.	Daughter	..	..	8,300	67	23	5	5	415	None.
M. B.	Daughter	..	..	8,200	70	23	5	2	164	None.
Mr. B.	Father (dead)	..	..	..	..	..	..	..	..	None.



Comment on Case 4. Although the mother had 16 per cent of eosinophils and a daughter 5 per cent, there was no indication of

any personal or family history of allergy, and parasitic infestation was ruled against by negative stool studies.

The unusual feature in this case was the excessive eosinophilic leukocytosis associated with asthma. Moderate eosinophilia is quite common, averaging from 3 to 7 per cent, with a normal leukocyte count, but there are only a few cases on record with eosinophilic leukocytosis of high degree. Herrick,[22] in 1911, reported a case with 77 per cent and a leukocytosis of 57,000 cells. Armand-Delille,[23] in 1927, described a case of asthma with a leukocyte count of 35,000 and 76 per cent eosinophils. It would be of interest to know if, in such cases, the excessively high eosinophilia might have been caused by an allergic state added to a preëxisting familial eosinophilia, as might well be suggested in this case.

Discussion. Every effort has been made to rule out the known causes of eosinophilia in the 4 families described. Transmission of the allergic state through several generations is quite commonly encountered, and, since eosinophilia is so closely related to allergy, the question is raised if eosinophilia without allergy, whatever its initial cause may be, may not be transmitted directly from one generation of a family to another. A review of the charts certainly suggests such an hereditary transmission of eosinophilia. According to clinical methods it seems fair to assume that allergic factors have been excluded. The possibility of trichinosis was more difficult to rule out. It is stated that the eosinophilia following trichinosis may last for years, but that it rarely lasts as long as 6 months. Blood counts were repeated after 1 year in 3 of these 4 families, and no essential change was noted in the percentages of eosinophilia. Both Klinkert and Armand-Delille emphasized the fact that eosinophilia in their cases persisted for many years.

Investigations have been exhausted in the effort to prove that trichinosis is not in any way related to the families reported—in the absence of history of any signs or symptoms of trichinal infestation, in the persistence of eosinophilia, by the negative Roentgen ray of muscle for trichinal cysts, and because of its presence in a few very young members of the families who, by reason of their ages, had never included pork in their dietary.

Skin diseases, specific blood disorders and chronic infections have been excluded in these families. In brief, the 4 families discussed in this paper present eosinophilia coincidentally in most of their members, clinically quite independent of any of the known causes of eosinophilia, and have been classified as examples of familial eosinophilia.

Summary. The term "familial eosinophilia" has been used by certain authors to connote eosinophilia in a family, whether caused by allergy, parasites or dermatoses, and by others to indicate its occurrence in families quite independent of a known cause. The latter usage has been adopted in this paper in classifying four

reports of familial eosinophilia. In conclusion, it may only be said that the significance of such an eosinophilia is as undetermined as the nature of the eosinophil, and at present one may only speculate upon an hereditary transmission.

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VASCULAR CRISES.*

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The term vascular crises is applied to sudden changes in the caliber of bloodvessels resulting either from contraction or from dilatation and causing transitory symptoms through malfunction or nonfunction of the part supplied by the affected vessel. Such crises are conditioned on the activity in the walls of the vessels of a nervous mechanism and in the medulla oblongata of a vasomotor center highly sensitive to reflex and direct stimulation.

The arteries of the body are normally in a state of tonus from which they change in either direction as conditions demand. Such changes constitute one of the important means the body has of adapting itself to the environment: heat produces dilatation, cold contraction of the vessels; during digestion more blood flows through

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the gastrointestinal tract and during exercise the muscles become hyperemic. Psychic influences also play an important rôle in the distribution of the blood—embarrassment leads to blushing, fear and distress produce pallor. In conditions of disease the same phenomena occur, only to an exaggerated degree. In a chill the surface vessels are strangled, the blood is driven back into the center of the body.

The nerves that supply the boodvessels with constrictor and dilator fibers are of sympathetic origin. The nerve endings fuse with the unstriped muscle cells in the middle coat of the vessels. Nearly all the bloodvessels of the body are supplied with such sympathetic fibers, except perhaps the arteries of the brain which, according to Bayliss,[1] have no vasomotor nerves running in their sheaths. More recent authors, however, especially Forbes and Wolff and Pender,[2] have shown that even the cerebral vessels are under the control of a nervous vasomotor mechanism, although this is probably less important than the general blood pressure as a regulator of the circulation in the brain.

It is usually held that the vasomotor nerves, barring a few special territories, are largely constrictor in action, that is, their stimulation either at the periphery or through the center in the medulla causes contraction of the vessels. It is highly probable that certain hormones act in the nature of vascular stimulants. The best known of these hormones is adrenalin. Another one may be the mysterious sympathin recently discovered by Cannon.

Dilatation of the bloodvessels has by many been looked upon as a passive process resulting from inhibition of the vasoconstrictor mechanism, but there is considerable proof that dilatation may be at times active. In animals dilatation of the bloodvessels can be produced through stimulation of the central end of the depressor nerve after all vasoconstrictor fibers have been severed. Such an experiment would imply the existence of a vasodilator center, but the convincing experiment applicable to man is still lacking.

General Vascular Crises. Vascular crises are general or local. General crises are exemplified by the sudden rises of blood pressure, so often seen in persons who are already hypertensive. The rise may be due to toxic, psychic or other causes and may pass off without any untoward symptoms. Frequently, however, such sudden general crises produce headache, dizziness, aphasia, monoplegia, hemiplegia, hemianopsia and even convulsions. It is at times difficult to determine whether the symptoms are the result of the high blood pressure crisis or whether some functional or anatomic change in certain brain territories precedes and causes the rise in blood pressure. The relation of these general crises to angina pectoris has recently been studied by Lewis, but while often accompanied or followed by anginal seizures, the sudden increase of blood pressure may not be the only factor.

Dilatational crises manifest themselves in a sudden fall of the blood pressure. In practice it is often difficult to decide how much of the fall of the blood pressure is due to vascular dilatation and how much to cardiac weakness. For example, in sudden coronary obstruction, in acute dilatation of the heart, in cardiac rupture there is a tremendous fall of blood pressure from direct depression of the cardiac function. The symptoms of dilatational crises closely resemble those of severe hemorrhage. They are pallor, sweating, sighing respiration, dizziness, thready pulse and at times unconsciousness. The condition is well exemplified by surgical shock. It is possible that some toxic agent such as histamin may play a rôle in the production of these symptoms.

Very marked shocklike crises occur at times in Addison's disease, probably as the result of a vasomotor paralysis or of vasodilatory stimulation or of both. Aside from true Addison's disease there is a functional adrenal depression,[3] which is also accompanied by a fall in blood pressure but less profound than that of true Addison's disease.

Local Vascular Crises. I shall now leave the subject of general vascular crises and consider local crises which possess a peculiar clinical interest of their own. In the majority of instances these crises are of spastic type and result from a constriction of the vessels. Such a constriction, I have already explained, is usually brought about through the mediation of the vasoconstrictor mechanism. It is quite possible, however, that contraction of the vessels can occur independently of the sympathetic nervous system. All the arteries and arterioles, even those of the brain in which the question of a vasomotor nerve supply is still perhaps not absolutely settled, have well-marked muscular coats and can undergo an intrinsic or myogenic contraction. The problem is similar to that confronting us in the heart. Here, too, we have a myogenic contraction, but one distinctly influenced by nerve impulses of extrinsic origin.*

Whatever the results of spastic contraction of vessels may be, they depend upon a variety of factors—the size of the vessel occluded, the duration of the spasm, the previous state of nutrition of the part and the possibilities of prompt collateral circulation. I once saw the pulse disappear completely at the wrist for a brief period through spasm of the radial artery without any noticeable after-effect. If the circulation is cut off for a sufficiently long time either functional or organic changes take place in the starved territory. Until recently the opinion prevailed that these results

* As is well known, one of the pioneers in the study of vascular crises is Professor Pal of Vienna. A few years ago I happened to be acting as Exchange Professor in the Peter Bent Brigham Hospital in Boston and on one of my morning ward rounds I had occasion to demonstrate a case illustrating vascular crises. During the course of my remarks I referred to Pal's work. At the end of the discussion, Dr. Christian introduced me to an elderly gentleman who had been one of my auditors—it was Professor Pal.

depended upon cutting off of the total blood supply, *i. e.*, of the nutritive material, but Barcroft and others have shown that the local deprivation of oxygen, for which I have proposed the term histanoxia,* is very damaging to the tissues.

Local vascular crises can occur in almost any organ or part of the body. The affected vessels may be normal, at least in appearance; often, however, they are the seat of varying degrees of arteriosclerosis. When not too rigid, diseased arteries are more sensitive to vasomotor influences than normal vessels. This accounts for the greater frequency of spasticity in such vessels. While they respond more readily to nervous and other influences, they return to their previous state more slowly than healthy vessels. Arteries subject to abnormally high blood pressure seem to be especially sensitive to vasoconstrictor influences.

Vascular Crises in the Brain. On account of the multiplicity of functions centered in the brain, vascular crises present a more varied picture than the same processes in other organs of the body. Monoplegia, hemiplegia, aphasia and convulsions are some of the possible motor crises. They occur most frequently in persons with hypertension, but they can also occur in those whose blood pressure is not markedly abnormal.

A number of years ago I was asked to see in consultation an elderly lady who had been seized suddenly and without warning with right-sided hemiplegia. Her daughter had arranged to go to Europe on a Government mission and wanted to know whether it was safe for her to leave her mother. During my examination I tested sensation with a pin and as I proceeded upward from the toes the patient suddenly exclaimed, "Oh, Doctor, I can move my foot; now my leg." Before I left the house the motion had completely returned in the paralyzed parts. The surprised patient credited me with superhuman powers. It is difficult to explain such a case on anything but a temporary angiospasm. The persistence of slight anatomic changes does not of necessity imply that the underlying cause was not a spasm, that it was a hemorrhage or a thrombosis. It is conceivable that highly irritable vessels might remain in a state of protracted spasm, which would lead to degeneration of the brain tissue.

It is a common error to consider convulsions in an individual of middle life who is not a true epileptic as uremic. This latter diagnosis is apparently strengthened by the finding of albumin in the urine immediately after the convulsive seizure. In many cases, however, there is between attacks no evidence either in the blood or in the urine of serious renal damage, so that it seems unlikely that the convulsions are due to uremia, whatever that mysterious

* From ἱστος, tissue; ἀνοξία, without oxygen. The word anoxemia sometimes used for local oxygen starvation connotes rather a general state of the blood than a local condition.

condition may be. The patient usually has a single convulsion at the time, but the attacks tend to repeat themselves at irregular intervals. The majority of patients in whom such convulsions occur are long-time sufferers from hypertension. The attacks, as a rule, pass off without any aftermath, although occasionally there is a transitory disturbance of vision, perhaps of speech or of mentality. I am inclined to believe that these attacks are of vascular origin due to a general hypertensive crisis. To distinguish them from true epilepsy, the term epilepsia tarda or senile epilepsy has been applied to the condition.[4] In treatment, the best results are obtained by free bleeding from the arm. Uremia and eclampsia are very similar to epilepsia tarda and may also represent vascular crises. The same thing applies to lead encephalopathy. There is, of course, something back of the vascular spasm, whether we are dealing with eclampsia, uremia or epilepsia tarda. There is some basic provocative agent, but whatever it is, it acts apparently not directly on the brain cells but on the circulation in the brain.

In addition to motor manifestations we meet with various sensory and psychic disturbances such as dizziness, tinnitus, hemianopsia, quadrant anopsia, amaurosis and headache. The so-called migraine headache has many features that suggest that it is an angiospastic condition. At times a spasm of the homolateral temporal artery is observable. What causes the spasm however is unknown—heredity, toxins, allergy, epileptic analogies crowd into the picture. Fundus and visual field studies during the attacks are desirable.

There are also evanescent psychic and psychomotor disturbances that are best explained on an angiospastic basis—sensory aphasia, amnesia, brief psychotic outbursts, etc.

Vascular Crises Affecting the Eye. These are quite common. I have already referred to their occurrence in migraine and in convulsions, but they may also occur independently. Redslob,[5] of Strasbourg, attributes retinal spasm to humoral causes, to changes in the ion concentration. His experiments seem to show that high concentration contracts and low concentration dilates the retinal vessels. Spasm is likely to be bilateral and lead to amaurosis. Barré[6] has described a syndrome characterized by vertigo, headache, paracousia and vasomotor phenomena of the head, which he attributes to pressure upon the sympathetic nerves by arthritic changes of the cervical vertebræ.

Vascular Crises in the Lungs. These undoubtedly occur, but we know little about them; at least we know little of vascular spasm in the lung. Vascular dilatation is an accompaniment of all acute inflammatory processes. There is, however, a condition, acute pulmonary edema, in which a vascular factor is highly probable. It is met with most often in hypertensive states, also in myocardial weakness and in mitral stenosis, and occasionally immediately after tapping the chest. This last variety usually follows too rapid

removal of a large amount of fluid in cases of hydrothorax of long standing. It seems to be brought about by a sudden rush of blood into the compressed lung, the altered vessels of which are not able to hold back the plasma. The patient may die, drowning as it were in his own juices.*

The pulmonary edema of hypertension or myocardial disease is usually attributed to a sudden weakness of the left ventricle. That, however, is not a complete explanation. I have seen pulmonary edema occurring simultaneously with a marked rise of general blood pressure and all the evidence of a powerfully acting left ventricle. It seems to me that there must be some change in the tonus of the pulmonary vessels, a sudden dilatation analogous to that of post-aspirational edema. Clinically the most striking features of acute pulmonary edema are intense dyspnea, *angor animi* not inferior to that of angina pectoris, an abundance of moist râles all over the chest and the expectoration, not invariably, of quantities of frothy fluid which on boiling coagulates completely.

The treatment is most satisfactory if promptly carried out. Three measures, separately or combined, rarely fail to bring the patient back from what looks like the brink of the grave—hypodermic injection of morphin and atropin, venesection and dry cupping of the chest. The last measure whatever its *modus operandi* is a procedure of indisputable value.

Vascular Crises in the Heart. Are the vessels of the heart liable to vasomotor spasm? This question opens up the endlessly discussed subject of the nature of angina pectoris. At the risk of being challenged, but as a means of saving space and time, I will say at once that I am a believer in the coronary origin of angina pectoris. It is scarcely necessary to speak to this audience of disease of the coronary arteries. Through the work of Herrick, Sutton and Le Count the subject is well known in Chicago. The angiospastic theory of angina pectoris seems to me to account best for the clinical picture and for the results of medicinal and surgical treatment. Slight sclerotic changes in the coronary arteries and in the aortic sinus render the cardiac vessels more irritable.

Vascular Crises in the Abdomen. Vascular spasm analogous to that at the basis of angina pectoris may occur in the abdomen, as pointed out by Ortner and by Osler. I have seen it in an interesting case: An elderly man came to me complaining of pain in the legs on walking a short distance. If he stopped, the pain passed off and he could walk without further trouble. The condition was clearly one of intermittent claudication. There was also a mild, readily controlled diabetes. After a year or two typical seizures of angina pectoris supervened. These eventually ceased entirely. Instead, the patient began to have sharp pains in the midepigastric

* This type of edema has been called edema by recoil.[7]

region for which no digestive error or other gastric cause could be found. From their character I attributed them to spasm of branches of the celiac axis. But that was not all. One day he noticed a peculiar disturbance of vision—in certain directions objects were blurred. A careful study of the visual fields revealed the existence of a quadrant anopsia.

The gastric crises of locomotor ataxia and the colic of lead poisoning have been attributed by a number of writers to angiospasm. I do not believe that this is the whole explanation, however. There must be some direct disturbance of the gastrointestinal canal to account for the constipation in lead colic and for the almost uncontrollable vomiting in tabetic crises.

Vascular Crises in the Lower Extremities. A few moments ago I referred incidentally to *intermittent claudication* which was so well described nearly 80 years ago by Charcot. While its essence is sclerosis of the arteries of the leg, it is probable that, in addition to the organic narrowing, there is a transient vasomotor spasm. The patient can walk only a short distance before the attack comes on, but if he waits a few moments the pain and numbness pass off and he is able to continue his walk with ease. Many patients with intermittent claudication have flat feet, practically all are heavy smokers; nearly 50 per cent of those affected are Russian Jews. Allen and Brown[8] found intermittent claudication to be an inaugural symptom of thromboangiitis obliterans. Of 200 cases one-half were Russian Jews, the other 100 being made up of a great variety of races, including native American. It is interesting that while in intermittent claudication arteriosclerosis is the rule, it is the exception in true angiitis obliterans. The diagnosis of intermittent claudication is easily made by the history and by finding absent pulsation in the dorsalis pedis and in the posterior tibial arteries. Roentgen ray examination reveals calcification along the course of the vessels; many patients, as I have said, have flat feet. The importance of recognizing it is that false diagnoses are often made, such as sciatica. One should, however, bear in mind the fact that bilateral sciatica is practically never sciatica. Diabetic neuritis may simulate intermittent claudication. Flat feet, metatarsalgia and rheumatism are some of the other diagnoses made. The prognosis depends largely upon the degree of angiospasm. The more spasm and the less sclerosis, the better the prognosis. Complete recovery is possible with proper treatment, but it must be borne in mind that intermittent claudication may be the forerunner of that horrible disease, thromboangiitis obliterans. In thromboangiitis (Buerger's disease) there is so much structural change in the arteries and veins that any considerable angiospasm is scarcely possible. However, it probably plays an intermittent rôle in those vessels in which occlusion by thrombosis has not proceeded too far.

Raynaud's Disease. Raynaud's disease is primarily an angiospastic affection. Not all cases so called are Raynaud's disease. Studies of the circulation, the effect of sympathectomy and anatomic investigations all indicate that the closure of the vessels is not due to endarteritis but to vasoconstriction. The cause of this constriction is unknown—endocrine imbalance, toxins, cold are some of the factors suggested. The disease is symmetrical and passes through stages of pallor and cyanosis with numbness and aching in the syncopal or pallid stage, and may end in peripheral gangrene.

Scleroderma is in part also an angiospastic condition; it is frequently accompanied or preceded by typical Raynaud's phenomena. But there must be a special element in scleroderma to account for the profound trophic changes that occur not only in the extremities but often in the face and chest. In a doctor's wife under my care at the present time not only are the extremities involved but the skin of the upper part of the chest and over the clavicles is becoming so tightly adherent that the patient cannot fully extend the neck. I may add that as far as my own experience is concerned, sympathectomy confers no permanent benefit; Adson has seen good results from ganglionectomy combined with sympathectomy; Leriche has recently advocated parathyroidectomy. The patient mentioned above is at present in Strasbourg for this operation.*

A local crisis of obscure nature is the so-called acrocyanosis, a bluish or reddish discoloration of the hands and feet. It is not like the asphyxial stage of Raynaud's disease for it persists, especially in cold weather. In all probability there is an angiospasm which reduces the capillary flow through the skin. There is no pain and there are no trophic changes.

A local *vasodilator* disturbance in the extremities is the condition known as *erythromelalgia* (Weir Mitchell's disease). The characteristic features of this are intermittent attacks of vasodilatation involving the hands and feet and associated with severe burning. During the attack the parts are red, hot, flushed, the veins dilated and throbbing.[10] Cold water and elevation give relief. A disturbance resembling erythromelalgia may appear as an early symptom of polycythemia rubra.[11]

The Cause of Pain in Angiospasm. Sir Thomas Lewis explains the pain in the extremities in intermittent claudication on the basis of an accumulation of metabolites. These metabolites or tissue poisons, the products of muscular activity, accumulate within the muscles and irritate the fibers directly, not however to the point of producing a muscular cramp. Lewis's experiments, simple but well planned, appear to support this view, but his interpretation does not seem to me to fit all cases of vascular occlusion. A sudden

* Longcope[9] has called attention to the occurrence of hypoglycemia in scleroderma.

thrombosis of a vein such as occurs in phlebitis is accompanied by instantaneous violent pain as if the individual had been hit with a brick. It seems hardly likely that the pain could be so prompt in onset and so severe in character if it were due to metabolites, for the accumulation of metabolites must take time. Furthermore, the sudden plugging of an artery, which does not interfere with the return flow through the veins, is usually also very painful. It is possible that in such cases the pain is produced by a sudden stretching of the artery proximal to the obstruction. This would bring the pain into analogy with biliary and ureteral colic.

Another argument in favor of an additional or a different interpretation than that given by Sir Thomas Lewis is found in the case of infarction. In certain organs, such as the spleen and kidney, acute thrombosis or embolism leading to infarction is often accompanied by violent pain and shock. In the case of renal infarcts I have seen the diagnosis of appendicitis made. The question of metabolites hardly enters in such cases.

I have under my care a patient with polycythemia rubra. Some time ago he was suddenly seized with agonizing pain in the left testicle. Upon examination I found what seemed to be a thrombosis of the veins. Subsequently he had a similar attack about the ankle, a sudden violent pain with redness and swelling, evidently also a thrombotic occlusion. In the case of the testicle the formation of metabolites is not likely to play an important rôle.

The conclusion seems warranted that the causes of pain in vascular occlusion, whether from spasm or plugging, are multiple:

1. The accumulation of toxic metabolites in active tissues, especially muscles.

2. Histanoxia, ischemia or local anoxemia.

3. Pressure upon sensory nerve endings in the walls of vessels either through stretching proximal to the obstruction or through an actual squeezing of the nerve endings during spasm. In both cases there would also result an inadequate blood supply to the vessel itself and to the surrounding receptor organs.*

Treatment of Vascular Crises. General angiospastic crises with rise of blood pressure are best treated by vasodilators such as nitroglycerin, erythrol tetranitrate, perhaps the choline derivatives, or by free bleeding. Rest, mental and physical, and good action of the bowels are also necessary.

Local Crises. The attempt must be made to relax the spasm. This can be accomplished by local heat, hot baths and by diathermy. Certain drugs have a value such as the nitrites, derivatives of cho-

* How the afferent impulses obtain cortical registration as pain is not definitely settled. In the case of the periphery of the body they may travel upward with the somatic nerves; in the case of the viscera that avenue is out of question. Afferent impulses from the heart course centrally largely by way of the pathways going to the first and second segments of the thoracic spinal cord.[32]

line, chloral hydrate and luminal; atropin, papaverin or morphin and atropin also may be used.

In severe cases affecting the extremities certain special measures may be indicated—the injection of foreign proteins such as typhoid bacilli or sympathectomy or ganglionectomy.

Vascular Dilator Crises. General dilator crises must be treated by rest, lowering the head and by vasomotor stimulants—adrenalin, pituitrin, ephedrin, strychnin, digitalis, caffein or coffee, or by transfusion of blood or by continuous venous infusion of glucose-salt solution.

In certain circulatory conditions in the lower extremities it is important from the standpoint of treatment to determine whether the condition is dependent upon the mechanical plugging of the vessel or upon vascular spasm. Scott and Morton[13] have proposed a test by means of which it is possible, except in the case of Raynaud's disease, to make this distinction. They find that general or spinal anesthesia, or local anesthesia produced by the injection of 1 per cent solution of procain, provokes a vascular dilatation with a consequent increase in surface temperature. If the defect in circulation is due to organic obstruction the local hyperthermia does not occur, but it does occur if the obstruction is due to angiospasm. A number of other tests have been designed to aid in differentiation and in planning treatment in cases of vascular obstruction of the lower extremities; for example, the histamin test and the triple cuff method of Pearse and Morton[14] determine the point to which the vessels are patulous.[15]

Thrombosis and Embolism. I have thought it proper to include under the general heading of vascular crises a few words about thrombosis and embolism which, though they are different phenomena, may produce a very similar clinical picture. The recent medical literature has much to say about the apparent increase in frequency of thrombosis and embolism. Most of the relevant literature comes from surgeons and pathologists who concern themselves chiefly with thrombosis and embolism in the lungs and limbs; but the clinician of mature years knows that thrombosis of the coronary arteries is increasing, whatever may be true of thrombosis elsewhere. Improvement in diagnosis is not the whole explanation. The increasing stress and strain of life is a most important factor; it certainly plays a part in the striking mortality of medical men from coronary disease. Diabetes, as Nathanson[16] has shown, is also a powerful factor in the production of sclerosis of the coronary arteries.

Embolic crises are common in the cerebral vessels. They may occur whenever any source of emboli exists in the body, such as venous thrombosis and subacute and vegetative endocarditis. But the process is especially common in mitral stenosis. Whenever I see a patient under 40 years who has suddenly had a hemiplegia

or a monoplegia, I first look for the cause in the heart. Naturally there are other possibilities, such as syphilis and hemorrhage, but in my experience I have found hemiplegia under 40 years most commonly due to mitral stenosis. The patient may not know that he has heart disease nor may there be a murmur when he is first examined because the murmur of mitral stenosis is fugitive. But whether the murmur is present or not, in nearly all cases there is a loud, snappy first sound that is highly suggestive of mitral stenosis.

While the symptoms of cerebral embolism may pass off in a few hours just as those of angiospasm, if they last longer than 24 hours they are apt to be more or less permanent. Furthermore, embolism in mitral stenosis is likely to recur. Both of these points are important to bear in mind in giving a prognosis. Embolism of the central artery of the retina is unfortunately a common condition occurring in the same circumstances in which we find cerebral embolism. A picture similar to embolism in the brain can be produced by cerebral thrombosis. While, however, in embolism the symptoms are sudden in onset, without any warning, in cerebral thrombosis there are often premonitory disturbances such as vertigo, headache and perhaps transient aphasia or weakness of a limb before the complete picture of hemiplegia appears. Improvement is very common in cases of thrombosis because the thrombus shrinks or becomes channeled and the circulation is in whole or in part reëstablished. Perhaps there is also a spasm in the vessels which recedes after a time.

Thrombosis and embolism are common in the lungs especially after operations and in chronic valvular and muscular heart disease. Postoperative pulmonary embolism from dislodgement of a clot in the operative field is usually a fatal catastrophe, although lately a few successful operations following the pioneer and courageous efforts of Trendelenburg have been reported.

Mesenteric thrombosis is not a very common vascular crisis. Prompt surgical treatment seems to be the only chance in the average type of case. The causes are obscure. Thrombosis and embolism of the extremities are frequent conditions—in arteriosclerosis, after operations, during the course of acute infections, in myocardial and valvular heart disease.

In the coronary vessels thrombosis is common and, as I have said, definitely on the increase. The results are variable. There may be instantaneous death, a lingering painful death, pain with subsequent congestive heart failure, or pain of variable duration with apparently full recovery. Other sequelæ such as rupture of the heart and cardiac aneurysm need not concern us now.

In conclusion I wish to say that there is much yet to be learned both clinically and experimentally about the bloodvessels and their important and somewhat neglected share in the circulation of the blood.

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THE ACCUMULATION OF IRON IN TUBERCULOUS AREAS.

III. Effect of Ferric Chlorid Injections on the Course of Development of Tuberculosis in Rabbits.*†

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Twenty years ago P. A. Lewis demonstrated that trypan red injected into the subcutaneous tissues of rabbits penetrated readily into caseous areas of tubercles in the lungs.[1] Similar observations with methylene blue were made on guinea pigs by DeWitt.[2] In previous communications[3,4] it has been shown that a vital dye (trypan blue) or iron in the form of its salt, ferric chlorid, when injected into the blood stream rapidly accumulates into an area of inflammation, where the substance is fixed and fails to drain to the tributary lymph nodes. Subsequent experiments[5,6] demonstrated that repeated daily intravenous injections of ferric chlorid in rabbits were followed by an accumulation of iron in tuberculous areas of the lungs. The iron was shown to accumulate in the caseous areas of tubercles. These experiments suggested that the accumulation of iron into tuberculous areas might alter the character or course of development of the disease. In a series of 16 rabbits inoculated with a bovine strain of tubercle bacilli repeated intra-

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venous injections of 0.25 per cent ferric chlorid for about 10 weeks were followed by a definite prolongation of the survival time of experimental animals. The animals increased in weight during part of the period of these injections. Both control and experimental animals died of generalized tuberculosis.

The present series of experiments were undertaken to determine first, whether the administration of quantities of ferric chlorid larger than had formerly been used and over a longer period would enhance the previous results on the increased survival time of tuberculous rabbits, and, in the second place, to obtain information on the effect of ferric chlorid injections on the development of the tuberculous lesion.

Experimental Method. Bovine tuberculosis was induced in weighed rabbits by the intravenous injection of a diluted saline suspension of a Ravenel strain. Twenty-seven days later the animals were divided into two groups. One group was kept to serve as control. Intravenous injections of 0.25 per cent ferric chlorid were started in the other group as follows: 1 cc. on the first day, 2 cc. on each of the 2 following consecutive days; 5 cc. on the fourth day and 10 cc. either every day with the exception of Sunday or else every other day for the 2 weeks following. Subsequently, injections of the ferric salt solution (10 cc. each time) were made 3 times a week for a period of about 17 weeks. In comparison with previous experiments[7] the period of injection was now doubled in its duration and some of the rabbits received almost 3 times as much ferric chlorid as was administered to rabbits of the preceding series.[7] The ferric salt solution was kept on ice when not in use. It was gently heated before each intravenous injection. The latter were always given very slowly. In spite of these precautions, ferric chlorid in the concentrations used was in a few instances found toxic for rabbits. Injections in these animals was followed by immediate death. Five animals were thus lost in the course of this study. It was found, as a rule, that small initial doses of the ferric salt solution increases the tolerance of the animal, so that subsequently considerably higher amounts could usually be injected without any untoward effect.

The rabbits used were all brindle in color and of the variety known to the animal breeders as "Flemish." The total amount of ferric chlorid injected in each rabbit varied from 130 to 620 cc. of a 0.25 per cent solution. Both experimental and control animals were weighed every week during the course of the experiment. The weighing was always performed at about the same time of day. The animals were so distributed that usually from 2 to 4 rabbits were kept in a single cage.

The results are based on a study of 36 rabbits; 20 of these were allowed to die of their disease in order to compare the survival time of control and experimental animals. A postmortem examination was performed on each rabbit. Usually specimens of lung, liver, spleen, kidney and bone marrow were fixed in 10 per cent formalin and stained with hematoxylin and eosin for microscopic examination. Sections of lung tissue of several rabbits were stained for the presence of tubercle bacilli. Tests for the presence of iron in tubercles of lung tissue were also performed (Prussian blue reaction). The remaining 16 rabbits of the series were sacrificed between the forty-fifth and the seventy-ninth day after inoculation with tubercle bacilli. In this way the extent of tuberculous lesions, particularly as observed in the lungs, was compared in control and experimental animals when both had had the disease for the same length of time.

Effect of Ferric Chlorid Injections on the Survival Time of Tuberculous Rabbits. The results of the experiments are shown in Table 1. The survival time of 10 control rabbits varied from 71 to 124 days, with an average of 94 days. The survival time of 10 experimental animals ranged between 89 and 190 days, with an average of 135 days. Granting the marked individual variations, it is clear, nevertheless, that the values of the survival time in the experimental group are consistently shifted to a higher level than in the controls. The average increase in survival time of experimental rabbits over that of controls as a result of repeated intravenous injections of ferric chlorid is 41 days. It is interesting to note that in the previous series[7] the average increase was 48 days. The results obtained in the present series are, therefore, essentially confirmatory. Larger quantities of ferric chlorid administered over a longer period of time have failed to produce more striking results in regard to prolongation of life than had previously been obtained.[7]

TABLE 1.—EFFECT OF FERRIC CHLORID INJECTIONS ON TUBERCULOUS RABBITS.

Control animals.				Experimental animals.				
Rabbit No.	Weight at beginning of experiment, gm.	Prussian blue reaction in tubercles of lungs.	Survival time after inoculation with tubercle bacilli, days.	Rabbit No.	Weight at beginning of experiment, gm.	Amount of 0.25 per cent ferric chlorid injected, cc.	Prussian blue reaction in tubercles of lungs.	Survival time after inoculation with tubercle bacilli, days.
3-00	2130	0	71	3-24	2360	240	++	89
3-66	2640	0	73	3-25	2320	280	++	90
3-29	2160	Trace	77	3-13	2280	270	++	97
3-21	2060	0	79	3-17	2710	340	++	112
3-27	2700	+ to ++	89	3-01	2780	420	++	119
3-18	2170	Trace	95	2-89	2740	420	+++	134
3-37	2800	+	102	4-13	2830	555	+	151
3-38	3115	0	105	3-15	2125	620	+++	182
3-35	2690	0	123	3-09	2315	526	++	184
4-20	2250	+	124	3-22	2920	610	++	190
Av.	...	...	94	...	...	...	...	135

Within a few minutes after dipping the lung tissue of the experimental rabbits into acidified potassium ferrocyanid an intense Prussian blue reaction appeared in the caseous centers of tubercles. The intensity of the color is indicated in Table 1 by the number of plus signs. The lung tissue of control rabbits either showed no Prussian blue reaction or, in some cases, it appeared to a relatively slight extent after the tissue had been bathed in potassium ferrocyanid for some time. In this connection it is to be noted that, as pointed out in a previous publication,[6] the Prussian blue reaction is occasionally positive in the caseous areas of a control rabbit, particularly if some degree of postmortem change has occurred.

The average change in weight, both in control and experimental animals throughout the duration of the experiment is represented in Chart I. The average weight in both groups was practically the same at the time of inoculation with tubercle bacilli. The control and experimental rabbits increased in weight for the first 3 weeks of the disease. The period of ferric chlorid injections was started during the fourth week. The experimental animals showed a slight increase in weight during the first part of this period. This was followed by a gradual fall in weight terminating in the death of the last experimental rabbit 27 weeks after inoculation with tubercle

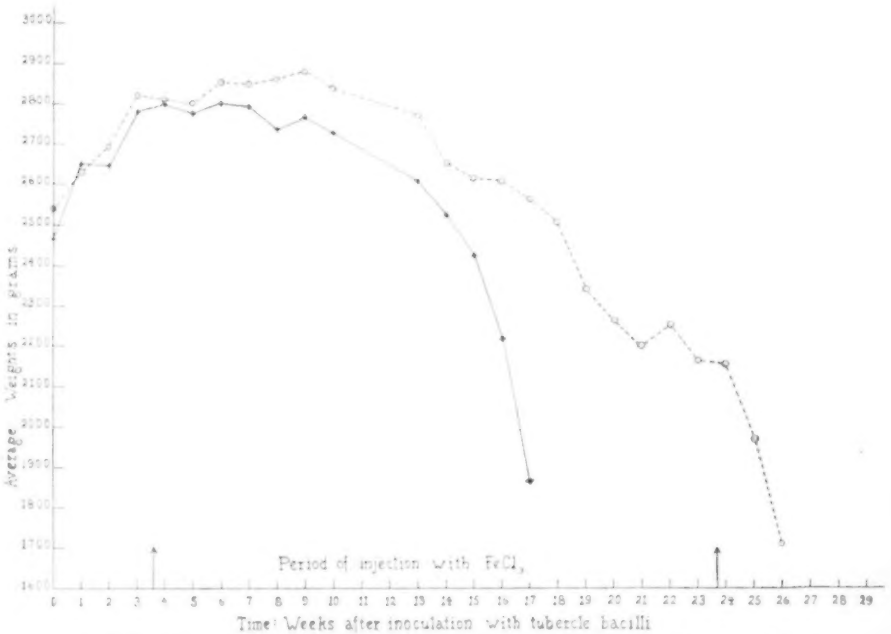

CHART I.—Average weight changes of tuberculous rabbits repeatedly injected with ferric chlorid, and of control tuberculous rabbits. ———x———, control rabbits; – – – o – – –, experimental rabbits.

bacilli. The control group showed no average increase in weight during the period when the experimental animals were receiving ferric chlorid injections. At the tenth week an abrupt fall in weight occurred, terminating in the death of the last of the control rabbits by the seventeenth week of the disease. The lag in the fall in weight of experimental rabbits, as seen in Chart I, is correlated with the increase in the survival time of this group (Table 1), and also as will be shown presently with a retardation in the development of tuberculous lesions in the lungs.

The average gain or loss in weight in both experimental and

control animals from 1 week to the next throughout the duration of the experiment is plotted on Chart II. The control group shows a progressive increase in loss in weight per week, beginning at the eleventh week and extending to the seventeenth week after inoculation with tubercle bacilli. The experimental group, on the other hand, shows a constant weekly loss in weight, though at a higher level than in the controls, during the period extending from the eleventh to the twenty-fourth week of the disease. At this time the injections of ferric chlorid were discontinued. This was followed by an abrupt fall in weight which terminated in the death of the last of the experimental animals about 3 weeks later.

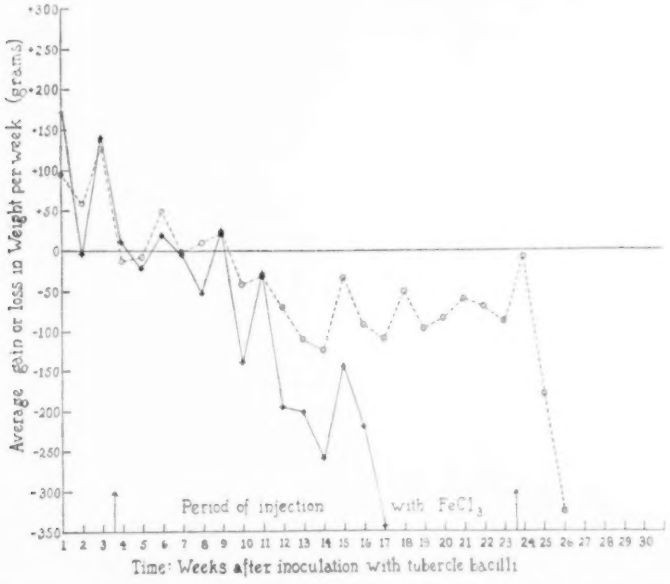

CHART II.—Average gain or loss in weight from week to week in tuberculous rabbits repeatedly injected with ferric chlorid, and in control tuberculous rabbits. ———x———, control rabbits; – – – o – – –, experimental rabbits.

Some of the organs, notably the lungs, in both the control and experimental rabbits were studied in the gross and microscopically at the time of death. A comparison of the pathologic appearance of the lungs revealed strikingly fewer tubercles in the 4 animals of the experimental series which survived for the shortest length of time (89 to 112 days, Table 1) as compared with the corresponding 4 of the control group (71 to 79 days). On gross examination, the lungs of these short-lived experimental rabbits exhibited discrete caseous foci in an irregularly congested parenchyma. Microscopic study showed, in addition to discrete caseating lesions with mono-

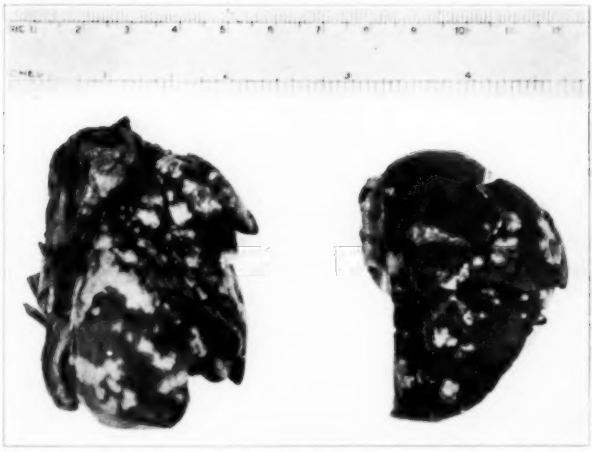

FIG. 1.—Comparison of lung of Rabbit 3–27 (control, 89 days) and that of 3–25 (experimental, 90 days). Both of these animals were allowed to die of their disease. Rabbit 3–25 had received by repeated intravenous injections a total of 280 cc. of 0.25 per cent ferric chlorid. Both of these animals died at about the same time; note the difference in the extent of the tuberculous lesions.

FIG. 2.—Lung of Rabbit 3–66 (control) and that of Rabbit 2–89 (experimental). Both of these animals were allowed to die of their disease. Rabbit 2–89 had received by repeated intravenous injections a total of 420 cc. of 0.25 per cent ferric chlorid. Note that the extent of tuberculous involvement found in the control lung (73 days) was approximately duplicated in the experimental group only at a considerably later period (134 days).

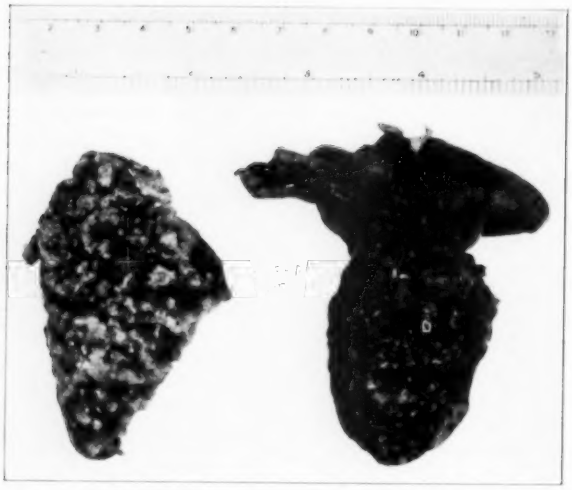

FIG. 3.—Lung of Rabbit 4–20 (control) and that of Rabbit 3–09 (experimental). Both of these animals were allowed to die of their disease. Rabbit 3–09 had received by repeated intravenous injections a total of 526 cc. of 0.25 per cent ferric chlorid. Note that the degree of tuberculous involvement in the lung taken from among the longest experimental survivors (184 days) is not greater than that found in the longest survivor of the control group (124 days).

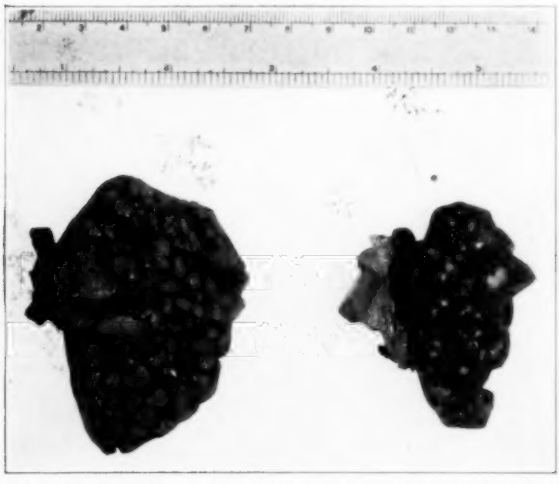

FIG. 4.—Comparison of lung of Rabbit 3–78 (control) and that of Rabbit 3–32 (experimental). Both of these animals were killed on the fifty-sixth day of their disease. Rabbit 3–32 had received by intravenous injections a total of 151 cc. of 0.25 per cent ferric chlorid. Although both of these animals were killed on the same day, the difference in the extent of the tuberculous lesions is striking. To illustrate the type of scale used in compiling the results of Table 2 the number of + signs indicate the extent of the lesions: Rabbit 3–78, control + + +; Rabbit 3–32, experimental +.

nuclear phagocytic infiltration, a considerable extravasation of red cells in several areas, alveoli plugged with serum and infiltration of polymorphonuclear leukocytes at the peripheries and centers of some tubercles. Considerable fibrin deposits were also observed. The lungs of those surviving for the shortest time in the control group were enlarged and consolidated with extensive confluent tuberculous lesions. Gelatinous exudation in alveoli and polymorphonuclear infiltration were infrequently seen in these 4 control animals. Judging by the degree of tuberculous involvement and, as described above, by the type of lesion in the lungs of experimental rabbits that had died at a relatively early date (Table 1), it is quite possible that the cause of death in these animals was in part the widespread exudative inflammatory reaction in the alveoli that one usually associates with the phenomenon of allergy. It is also to be noted that Rabbit 3–17 revealed at postmortem a massive infection in both ears, with an itch mite belonging to the Sarcoptes family. When the lungs of those dying first in the experimental group were compared with the lungs of control rabbits that had survived for an equal length of time, the difference both in number and extent of tuberculous lesions was striking. (Fig. 1.) The lung of the control (Rabbit 3–27, 89 days) shows numerous caseating foci with extensive confluence of lesions. The lung of the experimental (Rabbit 3–25, 90 days), on the contrary, shows fewer and discrete foci with relatively little confluence of lesions.

In comparing the degree of pathologic involvement in the control and experimental animals, it was found that the lung of a control surviving 73 days was best matched in the extent of its tuberculous lesions by the lungs of experimental rabbits that had survived 119 or 134 days. (Fig. 2.) The lungs showed massive consolidation with extensive confluence of lesions. Microscopic examination revealed in both cases a parenchyma replaced by large conglomerated caseating areas with diffuse mononuclear phagocytic infiltration at their peripheries. The control lung (Rabbit 3–66, 73 days) showed considerable invasion and plugging of the lumina of bronchioles primarily by mononuclear phagocytic cells. In the experimental (Rabbit 2–89, 134 days) a moderate proliferation of fibrous tissue was seen at the periphery of some of the tubercles. It is of interest to note that the rabbits of the experimental series surviving longest (184 to 190 days) failed to show more tuberculosis in the lungs than the last survivors in the control group (123 and 124 days). This fact is illustrated in Fig. 3.

In brief, comparison of the tuberculous involvement in the lungs of control and experimental animals seem to indicate that concomitantly with the accumulation of iron in caseous areas, there is a retardation in the progress of the lesions. These findings accord with the curves of average weight and with the increase in the survival time of the experimental rabbits (Table 1 and Chart I).

A brief summary of a few typical protocols of the postmortem examination (of the lungs in particular) is presented:

Protocols. *Rabbit 3–66. Control.* Survival time, 73 days; lungs enlarged, massive confluent caseating tuberculosis; lesions vary in size, averaging 10 to 12 mm.; kidneys studded with discrete caseating foci, 1 to 2 mm. in size; no gross evidence of tuberculosis in liver and spleen. Microscopic examination of lungs reveals large caseating areas in a parenchyma diffusely infiltrated with mononuclear phagocytes; lumina of bronchioles invaded in several instances largely by mononuclear cells from adjacent tubercles; few thrombosed vessels seen in lung parenchyma; liver cells show numerous hemosiderin-like granules within their cytoplasm; large amount of this same material in phagocytic cells of the spleen.

Rabbit 3–27. Control. Survival time, 89 days; lungs not enlarged; extensive confluent tuberculosis in many areas; lesions range between 1 mm. to several centimeters in size; microscopic examination shows confluent caseating lesions, many of which contain large deposits of calcium; diffuse mononuclear reaction replaces normal lung parenchyma. In some parts many of these cells and some polymorphonuclears plug the lumina of bronchioles; capillary congestion at the periphery of some of the tubercles; groups of alveoli filled with gelatinous exudate. Small foci of polymorphonuclear cells occasionally observed; metaplasia of alveolar epithelium into cuboidal type seen in several areas. No gross evidence of tuberculosis in kidney, liver and spleen.

Rabbit 3–35. Control. Survival time, 123 days; lungs small and show moderate amount of caseating tuberculosis in the right lung; confluence of lesions at base; left lung congested; discrete caseous foci throughout parenchyma. Microscopic examination shows alveoli plugged with gelatinous exudate containing many mononuclear phagocytes; lymphatics dilated with their lumina occluded by fibrinous strands; tubercles are either discrete or confluent; caseating material surrounded by epithelioid mononuclear phagocytes and lymphocytes; polymorphonuclear infiltration fairly extensive; fibrous proliferation about some of the lesions; a few alveoli plugged by extravasated red cells; numerous tubercle bacilli in caseous material. No gross evidence of tuberculosis in kidneys, liver and spleen. Considerable number of hemosiderin-like granules within liver and Kupffer cells.

Rabbit 3–13. Experimental. A total amount of 270 cc. of 0.25 per cent ferric chlorid injected; survival time, 97 days; lungs small; left lung congested; few and small discrete tubercles, averaging in size 3 to 4 mm.; no confluence of lesions; trachea occluded by viscid, yellowish suppurative material. Microscopic examination reveals large numbers of alveoli plugged with gelatinous exudation. Considerable amount of delicate fibrinous deposits in some of the alveoli and within the lumen of vessels; lesions contain many polymorphonuclear leukocytes; tubercles made up of caseous centers with collections of epithelioid cells interspersed with polymorphonuclear cells about them; engorgement of capillaries and extravasation of red cells seen in a number of areas; few discrete foci in kidneys; spleen and liver not remarkable.

Rabbit 2–89. Experimental. A total amount of 420 cc. of 0.25 per cent ferric chlorid injected; survival time, 134 days. Lungs enlarged; massive consolidation with confluent caseating tuberculosis throughout both lungs. Microscopic examination shows large confluent caseating areas in a parenchyma diffusely infiltrated with mononuclear phagocytes; moderate connective tissue proliferation at the periphery of tubercles. Kidneys studded with miliary foci; large conglomerated lesions in right kidney, about 5 mm. in size; hemosiderin-like granules in cells of glomerular tufts; similar material scattered in some of the cells lining many tubules. These granules

produced a positive Prussian blue reaction when sections were treated with acidified potassium ferrocyanid; this same hemosiderin-like material seen scattered within liver cells, Kupffer cells and mononuclear phagocytes in the bone marrow.

Rabbit 3–22. Experimental. A total amount of 610 cc. of 0.25 per cent ferric chlorid injected. Survival time, 190 days; lungs studded with discrete caseous foci, ranging in size from 1 to about 8 mm., the majority being 2 or 3 mm.; relatively little confluence of lesions. Microscopic examination shows conglomerated tubercles with large proliferation of mononuclear phagocytes at the peripheries; a moderate amount of fibrous tissue proliferation; large calcium deposits within some caseating areas; clumps of tubercle bacilli scattered within the peripheral portion of caseous material. Kidneys show rare discrete foci. No gross evidence of tuberculosis in liver and spleen.

Effect of Ferric Chlorid Injections on the Extent of Tuberculous Lesions in the Lungs. As pointed out at the beginning of this paper, an additional 16 rabbits were inoculated intravenously on the same day and with the same suspension of bovine tubercle bacilli as the animals in the series discussed above. These rabbits were killed at various intervals of time This was done in order to compare the progress of the disease, as indicated by the extent of the pulmonary lesions, in the control and experimental animals. In addition, 8 rabbits taken from the preceding group of control and experimental animals, all of which had died early of their disease, were studied in regard to the extent of the lesions. Thus 24 animals in all were used, 12 of which had had repeated intravenous injections of 0.25 per cent ferric chlorid beginning on the twenty-seventh day after inoculation with tubercle bacilli. The interval between the injection of tubercle bacilli and the death of the animals ranged between 45 and 97 days. The lungs of an experimental animal were compared with those of a control that had had the disease for approximately the same interval of time.

TABLE 2.—EFFECT OF FERRIC CHLORID INJECTIONS ON THE EXTENT OF TUBERCULOUS LESIONS IN LUNGS.

Control animals.				Experimental animals.				
Rabbit No.	Weight at beginning of experiment, gm.	Interval between injection of tubercle bacilli and death of animal, days.	Extent of tuberculous involvement	Rabbit No.	Weight at beginning of experiment, gm.	Interval between injection of tubercle bacilli and death of animal, days.	Amount of 0.25 per cent ferric chlorid injected, cc.	Extent of tuberculous involvement.
3–36	2660	46	+	3–11	2520	45	130	Trace
3–78	2560	56	+++	3–32	2405	56	151	+
3–10	2535	59	++	3–16	2515	59	172	+
1–17	2040	60	++	3–33	2175	61	180	+
3–66*	2640	73	+++	3–30	2665	73	240	++
3–29*	2160	77	+++	2–95	2195	76	200	++
3–34	2720	78	++	3–23	2780	78	197	+
3–14	2510	78	+	3–03	2310	78	210	+
3–88	2195	79	++	3–05	2420	79	176	++
3–21*	2060	79	+++					
3–27*	2700	89	++	3–24*	2360	89	240	+
				3–25*	2320	90	280	+
3–18*	2170	95	++	3–13*	2280	97	270	+

Trace = small, discrete caseating lesions averaging about 2 to 3 mm. in diameter. + = discrete, caseating lesions averaging about 5 mm. in diameter; no confluence of lesions. ++ = numerous caseating foci with some confluence of lesions. +++ = lungs enlarged, massive caseating tuberculosis with extensive confluence of lesions.

* These rabbits were allowed to die of their disease; all others were killed.

The results of this study are summarized in Table 2. An explanation of the comparative scale used accompanies the table. It is clear that in all cases with the exception of 2 rabbits (*i. e.*, in 83 per cent of the animals) the tuberculous lesions in the lungs were less extensive in the experimental than in the control group. Fig. 4 illustrates the type of results obtained. The observations indicate that repeated intravenous injections of ferric chlorid retard the development of tuberculous lesions in the lungs of rabbits inoculated with a bovine strain of tubercle bacilli.

Microscopic examination of lungs of control and experimental rabbits substantiated essentially the results found in the gross. A brief summary of a few protocols is presented.

Protocols. *Rabbit 3–36. Control.* Killed 46 days after inoculation with tubercle bacilli; large areas of conglomerated caseating foci with diffuse mononuclear phagocytic infiltration at periphery; no gelatinous exudation within alveoli.

Rabbit 3–11. Experimental. Killed 45 days after inoculation with tubercle bacilli; a total of 130 cc. of 0.25 per cent ferric chlorid administered; small discrete foci of mononuclear cells with little caseation; no gelatinous exudation within alveoli.

Rabbit 3–78. Control. Killed on fifty-sixth day of the disease; very extensive confluence of caseating lesions with diffuse mononuclear infiltration at the peripheries; large numbers of bacilli in caseous material.

Rabbit 3–32. Experimental. Killed on fifty-sixth day of the disease; a total of 151 cc. of 0.25 per cent ferric chlorid administered; lungs show discrete foci of mononuclear cells with practically no caseation and an absence of confluence.

Rabbit 3–10. Control. Killed on fifty-ninth day of the disease; lungs show very extensive caseating lesions which are confluent; large calcium deposits in caseous areas; moderate fibroblastic proliferation about the lesions; extensive areas infiltrated with mononuclear phagocytes; no tubercle bacilli found.

Rabbit 3–16. Experimental. Killed on fifty-ninth day of the disease; 172 cc. of 0.25 per cent ferric chlorid administered; lungs show many large foci of caseation with diffuse infiltration of mononuclears at their periphery; small amount of confluence and no calcium deposits; few acid-fast organisms found in the lesions.

The observations reported in this communication indicate that concomitantly with an accumulation of iron from the circulating blood into caseous areas of tubercles, the course of the disease in the rabbit is protracted as evidenced both by a retardation in the development of the tuberculous lesion and by a definite increase in the survival time of the injected rabbits. The increase in the survival time confirms the findings obtained in a previous series of animals.[7] It remains to be seen whether the effects obtained are entirely due to the accumulation of iron in tuberculous foci; for it is conceivable that there may be other factors involved in producing the results. Whether repeated intravenous injections of ferric chlorid will produce similar effects on animals other than the rabbit and infected with different types of tubercle bacilli, remains also to be seen.

Further studies are being conducted to investigate these questions.

Conclusions. Repeated intravenous injections of ferric chlorid are followed by an accumulation of iron in caseous areas of tubercles and by a definite increase in the survival time of tuberculous rabbits.

Studies of weight changes and comparison of the pathologic involvement in the lungs of the control and experimental animals at various intervals indicate that the intravenous administration of ferric chlorid protracts the course of the disease.

Repeated intravenous injections of ferric chlorid retard the development of tuberculous lesions. This is indicated by comparing the extent of the pulmonary lesions in control and experimental animals having had the disease for the same length of time.

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TIME AND DOSAGE AS FACTORS IN THE CURE OF SYPHILIS.

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Although routine antisyphilitic treatment may vary somewhat in different clinics, a fundamental uniformity in schedules emphasizes the general acceptance of certain factors governing the successful administration of antisyphilitic remedies. The physician is armed with potent specific drugs but he recognizes that the cure of the patient will result from the interaction of a number of forces. The tissue defense mechanism will contribute substantially to the therapeutic result and a lapse of time during which this defense action may evolve is one necessary factor in the cure of the disease.

Thus it has come to be recognized that a "therapeia magna sterilisans" of Ehrlich rarely exists in practice and that direct spirocheticidal action is not solely responsible for the effect obtained. It is, therefore, of prime importance for the physician treating

patients suffering from syphilis to keep clearly in mind the relationships which undoubtedly exist between dosage, lapse of time and therapeutic effect. He should also be in a position to appreciate and evaluate the disadvantage of any great deviation from optimum schedules of treatment. Clearer conceptions of the interplay of various factors are always obtained if the information available can be reduced to graphic form; in other words, if it can be plotted. Such is the purpose of this paper.

In 1919[1] and 1921[2] the author published data on therapeutic results obtained from the administration of arsphenamin in the

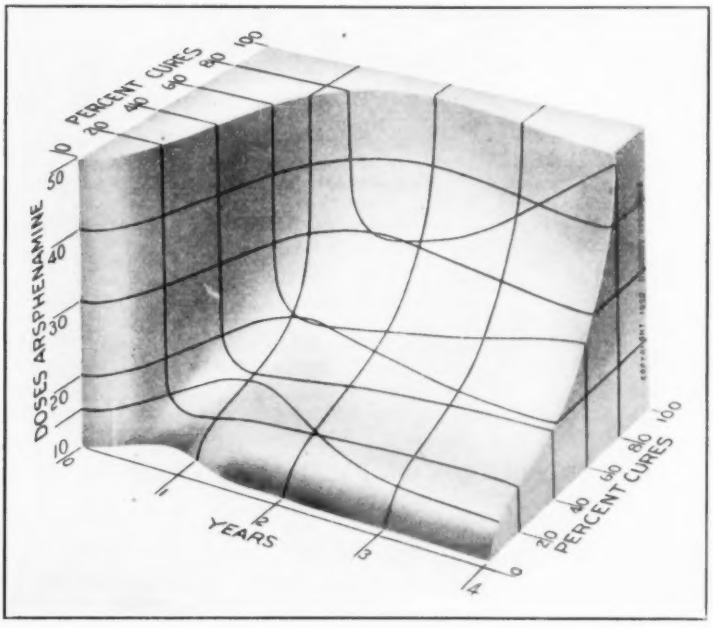

FIG. 1.—Therapeutic surface. Seropositive, primary and secondary syphilis.

treatment of syphilis. Further data resulting from new clinical material together with later information about the cases which had already been studied were subsequently collected but not published. In 1926 Moore and Keidel[3] published several papers on the treatment of syphilis presenting similar data in a different form, while from time to time other publications have appeared which contribute to this general data.

In this paper we tabulate results obtained at the Pennsylvania Hospital, and from this and from other available information we develop a graphic portrayal of the therapeutic effect to be expected from arsphenamin in the treatment of syphilis. Since this graphic

representation involves three factors it must be drawn in three dimensions and it results in a surface. Such surfaces are portrayed in Figs. 1 and 2.

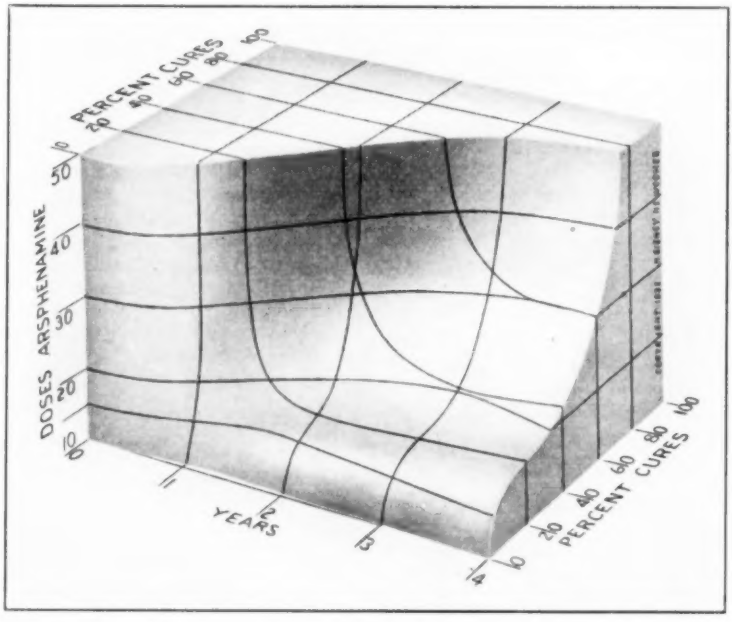

FIG. 2.—Therapeutic surface. Late syphilis.

Surfaces in three dimensions, being the locus of "cured" patients treated with varying amounts of arsphenamin during varying periods of time. The vertical axis represents doses of arsphenamin, starting with 10 doses for the base line. The horizontal axis represents time in years. Depth represents cures in per cent for an average large group of individuals. The intersections with the surface of planes passing through the enumerated subdivisions along the coördinate axes give curved lines which serve as reference lines for the location of data points on the surface.

Table 1 gives data for patients having seropositive, primary and secondary syphilis. Table 2 gives similar data for patients having tertiary syphilis. The lesions in tertiary syphilis are much too varied to allow of any simple or certain classification into subgroups. Most of the patients with late syphilis came to the syphilis clinic from the dispensary of a general hospital and are typical of the various manifestations found at this stage of the disease. Very few of the patients tabulated had neurosyphilis, about 3 per cent were tabetic and there were no cases of general paresis.

The technique employed for the Wassermann reaction of the individuals tabulated included the use of both an acetone insoluble and a cholesterinized alcoholic extract antigen. For patients who have received treatment the latter antigen is the most reliable, but it will sometimes give a positive reaction in the case of patients not having syphilis. The proper interpretation of the Wassermann reaction requires considerable experience and it is impossible to put in writing the criteria on which judgments are to be based. The author has previously published observations on the Wassermann

reaction[4] and given examples of confusing cases.[1] Such examples could be multipled many times but no charts can replace a study of the patients themselves.

TABLE 1.—SEROPOSITIVE, PRIMARY AND SECONDARY PATIENTS.

	6 to 12 mos., over 10 doses	12 to 18 mos., under 25 doses	Silver arsphenamin	18 mos. or over	Over 30 mos.	H.S.N., 1918 cases	H.S.N., 1920 cases	Over 25 mos., over 35 doses
Average time, mos.	9	12.5	15.5	21.4	46.4	8	18	43
Average doses	15.4	14.7	23.5	18	17.6	21	27	44.8
Per cent negative	28.5	28.5	50	61	73	46	85	33
Per cent doubtful	28.5	21.5	30	6	0	0	0	8
Probable cures, per cent	12*	20*	60	60	73†	35	75	35/85
Number of patients	14	14	20	18	11	13	13	12

TABLE 2.—SEROPOSITIVE TERTIARY PATIENTS.

	6 to 12 mos., over 10 doses	12 to 18 mos., under 25 doses	Silver arsphenamin	18 mos. or over	Over 30 mos.	H.S.N., 1918 cases	H.S.N., 1920 cases	Over 36 mos., over 25 doses
Average time, mos.	9.3	13.6	19	21.4	42.1	11	27	50
Average doses	16.4	16.2	26.5	20.5	20.6	22	38	45.2
Per cent negative	0	4	10	10.5	43	0	47	20
Per cent doubtful	16	10	20	27	10	0	18	21
Probable cures, per cent	0	3	20	22	45	0	50	35/70
Number of patients	43	50	80	48	30	17	17	24

The patients represented in the tables are divided into groups of individuals who have had very roughly equal amounts of treatment over equal intervals of time. The figures in the columns give for each group the average number of months under treatment, the average number of doses received, the per cent of individuals who have become apparently permanently negative, the per cent who are negative without any evidence that they are permanently so, and an estimate as to how many of both classes of patients will continue negative. The last line gives the number of patients in each group.

Except for Columns 6 and 7, no patients are represented twice. The columns headed H.S.N. tabulate previously published data. The last column tabulates patients who were particularly stubborn in yielding to treatment and, therefore, includes an undue proportion of incurables. For these patients 2 figures are given for probable cures: 1 for the group and 1 for a hypothetical representative group.

Although little is definitely known as to the significance of a continuously negative Wassermann reaction, it is probable that repeatedly negative reactions indicate improvement when they are obtained in patients previously positive and clinically well under treatment. When the reactions are continuously negative over a period exceeding 1 year it may be assumed that a permanent change in the patient's condition has taken place and that the Wassermann reaction will continue to be negative. Although there are exceptions to this statement, for statistical purposes it is useful to speak of such patients as "cured."

In the accompanying tables "doubtful" indicates patients who appear clinically cured and have a Wassermann record showing definite improve-

* These estimates are obviously too small to fit the surface (Fig. 1); 25 and 30 would be more appropriate numbers and are not inconsistent with the data of the third and fourth lines.

† This number is too large to fit the surface but is less out of line when consideration is taken of the fact that the long period of time refers to an observation period rather than a treatment period.

ment toward the negative but not negative for a sufficiently long period of time to be termed "cured."

Individuals tabulated in the first two groups were under observation only a short time. It is not possible to classify any of these as permanently negative but an estimate is made based on the negative Wassermann record and the clinical picture for that time.

The patients in the third column received silver arsphenamin. In the second and third columns from the last of both tables data from previously published cases is used.[1,2] In some instances these patients have been followed for a longer period of time and their subsequent history has then been consistent with the data first published.

In the last column of each table are placed the cases particularly stubborn in yielding to treatment. They differ from all the other groups in the large amount of arsphenamin administered and the time under treatment. Such a group tends to include more than its just proportion of incurables as more fortunate patients leave the clinic as they improve. For this column, therefore, two figures are given for the number of probable cures, one for the actual group and one for a hypothetical representative group, the latter figure being used in the graphic analysis.

It is possible by reference to the treatment data originally published in detail[2] to extend the amount of statistical information to time intervals and dosages other than those set forth in the tables.

In the majority of cases the tertiary patient who is likely to be cured becomes negative during 3 years of treatment. At the end of the first year about 3 per cent of the patients tabulated appeared to be negative; while at the end of the second year, depending on the amount of treatment received, the number of cures ranged from 25 to 40 per cent. The group of patients (Column 4, Table 2) who were only 22 per cent negative received insufficient treatment. There is no representation in this table of a group who had received the ideal treatment of 30 doses in 2 years but by interpolation from the table it is very probable that about 40 per cent of such patients would be negative at the end of 2 years, while at the end of the third year cures should increase to approximately 60 per cent. As a matter of fact those patients listed in the next to the last column of Table 2 showed approximately 40 per cent of cures at the end of 24 months.

The data of Table 1 for seropositive, primary and secondary syphilis are subject to somewhat the same analysis. The figures in the fifth line for probable cures were made before the concepts set forth in this article were developed and the first 2 figures, 12 and 20 of this line, are obviously underestimates.

As additional data used in developing the surface of Fig. 1 we have not only the general information which may be deduced from generally used therapeutic schedules, but we have specific information given in the article by Moore and Keidel.[3]

Moore and Keidel, in their article, state: "Only 10 per cent of patients receiving 8 or less doses of arsphenamin without mercury were cured. When two courses of arsphenamin plus mercury were given 37 per cent were cured, after three courses 56 per cent and after four or more courses 79 per cent of probable cures were obtained. With the utmost coöperation

on the part of the patient, and painstaking treatment and follow-up on the part of the physician, it appears possible to cure 100 per cent of patients with seronegative primary syphilis, but only 80 to 95 per cent of those with seropositive primary or secondary syphilis. The refractory 5 to 20 per cent seem likely in spite of the utmost efforts of therapy to develop late syphilis, especially neurosyphilis."

There is no essential discrepancy between this information and that obtained at the Pennsylvania Hospital. Moore and Keidel's routine treatment, which consists in administering arsphenamin in courses of 6 doses interrupted by rest intervals of 4, 6, 8 or 10 weeks, fixes within certain practical limits the number of doses which the patient may receive in any given period of time and, therefore, determines the time interval which must elapse before the cures spoken of by these authors could be effected. The data of Moore and Keidel are, therefore, subject to tabulation in a form similar to that of Table 1.

In this paper it is assumed that the patient has the benefit of mercury or bismuth in addition to arsphenamin therapy. We are also justified in assuming that the arsphenamin was of good quality and given in optimum doses.

A consideration of arsphenamin as the chief therapeutic agent involves taking account of the number of doses given, the time interval of treatment and the result in percentage cures. Plotting therapeutic effect as a function of time and number of doses results in a surface in a three dimensional space.

In the following discussion it will be seen that the actual quantitative figures become relatively unimportant in relation to the character of the surface which they determine and that the interpretation of the form of the surface gives information of much greater value than any consideration regarding the exact accuracy of the data from which it is obtained, the form of the surface being, in fact, remarkably independent of the accuracy of the data.

Seropositive Primary and Secondary Syphilis. Almost universally it is considered good practice to give such individuals "intensive arsphenamin treatment," *i. e.*, at least 1 dose a week with relatively short rest intervals between courses, the rest intervals increasing in length from time to time.* If the known data be plotted it becomes apparent in the first place that a small number of doses, for instance, 10, cannot give as a maximum much more than 10 per cent of cures. These doses would have been given in the first 3 months. Experience indicates that there will be some delay in the Wassermann reaction becoming negative, that is, the effectiveness of this treatment becomes apparent only after the lapse of a certain period of time.

If the doses are spread too thinly over the first year the number of cures will fall off and as the time over which the doses are distributed is increased a less and less number of patients will be

* For a scheme of treatment, see H. N. Cole.[5]

cured; finally no cures can be added by inadequate subsequent treatment of those who failed to become negative following the first 2 or 3 doses.

If we increase the number of doses available to 15, the time interval lengthens somewhat and the therapeutic effect is greatly increased, the maximum being about 35 per cent.

It is pretty well established that this optimum of 35 per cent of cures can be obtained only when the arsphenamin is given according to the well-established regimen of weekly doses, interspersed by proper rest intervals during which mercury or bismuth is administered. Practical time considerations fix the maximum effect obtainable somewhere toward the end of the first year. It is obvious that as the doses are spread more and more thinly over the first and subsequent years the number of cures effected will drop off.

Thus the "therapeutic surface" shows a hollow or valley extending through the latter part of the first year and the whole of the second year. Beyond this time a decreasing therapeutic effect is obtained with any given number of doses. Prior to this time, concentrating the doses into a shorter time interval gives less beneficial results. Complete sterilization by direct spirocheticidal action is only obtainable early and in relatively few individuals. Too massive treatment defeats its own purpose, and deprives the individual of natural tissue defense in the later stages.

Such reasoning fixes the forms of the curves for 20, 30, 40 and 50 doses of arsphenamin. If the percentages were different the form of each curve would nevertheless be the same. As the doses are increased the maximum therapeutic effect gradually shifts in time to be attained after about 2 years' treatment with 50 doses. The surface must obviously be continuous and regular and this applies not only in the direction of increasing time but also in the direction of increasing doses.

Let us consider sections of the surface made by planes corresponding to the first, second, third and fourth years. They give the vertically directed curves of Fig. 1. The form of these curves at the top and bottom, as seen when looked at from the end of the block, is fixed by considerations outside of any data. For instance, in the case of the 1-year curve the slope must be approximately vertical from 40 doses onward and must, indeed, turn on itself eventually as the number of doses is indefinitely increased. Under such circumstances toxic symptoms would eventually out-balance any therapeutic effect. Thus each of the curves as it approaches the 50-dose line and is extended to the 60-dose line must have a very steep slope, for additional therapeutic effect is not obtainable. Similar considerations hold for the interval between the first and tenth doses.

In fact a study of the possible degrees of freedom of the surface reveals that if all factors operating are taken into consideration its

form, *i. e.*, its shape, cannot be much different from that depicted in Fig. 1.

Treatment of Late Syphilis. The treatment of late syphilis presents a different situation. The sterilizing or spirocheticidal action of arsphenamin in such cases is less effective and massive treatment is no longer desirable. The defense mechanism of the patient and the resolution of the lesions plays a more important part and lapse of time must be allowed for such reaction to develop and become effective.

The situation in early syphilis after the first failure to produce complete sterilization is admirably stated by Brown and Pearce:[6] "During the early stages of acquired syphilis our efforts may be concentrated on the destruction of the parasites, but once a characteristic lesion has been developed it is useless to attempt to prevent a systemic distribution of organisms; every part of the body is potentially infected, but it is still possible to prevent the localization and growth of spirochetes in inaccessible foci and to prevent the development of lesions which afford more or less protection against the action of spirocheticidal agents. Fortunately, Nature aids us in this in a most effective way through the adaptation of different tissues to the growth of spirochetes. Thus, the first focal infections occur in tissues that offer no great hindrance to drug action, and with the exception of the chancre, the early lesions are readily permeated by therapeutic agents."

Speaking of the more advanced stages of syphilitic infection, Brown and Pearce call attention to the increased complexity of the problem. The organisms have become established in inaccessible locations, such as the cardiovascular and central nervous systems: "It is obvious that if vigorous treatment with parasiticidal agents is begun in the early stages of syphilis and continued systematically without accomplishing the desired result, there is little hope that persistence in the use of the same methods may prove successful when the obstacles to success have been greatly increased."

The data collected at the Pennsylvania Hospital quite clearly indicate the importance of time as a factor in treatment. Here again we have to take account of a maximum obtainable therapeutic effect (of about 75 per cent) reached with approximately 50 doses of arsphenamin at the end of a 4-year interval. Additional treatment in that interval will not raise this percentage. If the 50 doses are all given during a 2-year interval the cures are decreased to about one-half the maximum obtainable.

The surface shown in Fig. 2 represents what may be expected from various numbers of doses given in different time intervals. Fifteen doses produce much less effect than in cases of primary and secondary syphilis. They may be spread over a much longer interval and still evoke the maximum effect. When the number of doses is increased to 20 the cures jump to around 35 per cent provided the doses are spread over a sufficient period of time.

The vertical curves of Fig. 2 indicate the therapeutic effect obtainable with different numbers of doses administered over periods of 1, 2, 3 and 4 years. The same considerations hold, although to a

different degree, for these patients as for the patients with early syphilis. There is a marked difference between the two sets of curves due to the fact that tertiary syphilis is not amenable to treatment in a short period of time. No matter how much arsphenamin is given in the first year, our statistical data indicate, and many clinicians have long since reached the conclusion, that much less benefit will be obtained than from treatment continued during the second and third years. This is understandable in view of the nature of the curative process as described by Brown and Pearce,[6] and is given expression in schedules of treatment by Stokes,[7] Moore,[8] Harrison[9] and others.

Returning to Fig. 1 for early syphilis, we see that the patients who were not cured by the early treatment become in fact cases of tertiary syphilis. The curative effect in the third and fourth years, particularly in the fourth year, is thus limited to figures corresponding to those found to hold in the treatment of late syphilis and shown by the surface of Fig. 2, third and fourth years. This consideration coupled with the mathematical necessity of making the surface regular determines in Fig. 1 the shape of the surface in the third and fourth years.

It is impossible in a short descriptive explanaton to discuss all of the factors which necessarily operate to fix the form of these therapeutic surfaces but enough has been said to indicate that their general character is fixed within sufficiently narrow limits so that the surfaces as drawn must present the essential facts.

Summary. The "therapeutic surfaces" of Figs. 1 and 2 enable one to visualize in a striking fashion many aspects of the relationships between time and doses and expected cures of cases of syphilis. It would seem that *the proper treatment of primary and secondary syphilis involves the administration of 30 to 50 doses of arsphenamin* in appropriately spaced courses *over a period of 1½ to 2 years. Increasing the total number of doses above 50 is of no benefit while more than 30 given in the first year produce no additional cures.*

In the treatment of tertiary syphilis if 50 doses of arsphenamin are available, the best results will be obtained if these be given over a 4-year period rather than over a 2-year period. Such a schedule may perhaps be facilitated by spacing the injections in each course 2 weeks rather than 1 week apart. A considerable dosage of arsphenamin concentrated into the first year or two of treatment is of no benefit to the patient and is both discouraging and economically disadvantageous.

These facts and the ready visualization of expected therapeutic result afforded by the surfaces enable the physician to lay out the most rational plan of treatment with a clear appreciation of just what may be expected when for one reason or another it is not possible to follow a dosage schedule which should give optimum results.

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MACROSCOPIC EXAMINATION OF THE BLOOD.

DISCUSSION OF ITS VALUE AND DESCRIPTION OF THE USE OF A SINGLE INSTRUMENT FOR THE DETERMINATION OF SEDIMENTATION RATE, VOLUME OF PACKED RED CELLS, LEUKOCYTES AND PLATELETS, AND OF ICTERUS INDEX.

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FROM the days of Hippocrates and of Galen until the advent of microscopy, physicians were greatly concerned with the gross appearance of the blood. The ancient theory of pathology, the doctrine of the four humors was, indeed, founded on the observation that blood drawn from an unhealthy individual differs conspicuously from normal blood after clotting. As Fahraeus[1] has pointed out, the four humors correspond to the four layers which can be seen when a fairly large quantity of blood is drawn from a patient and allowed to clot, namely, (1) a lowermost dark portion (melancholia) composed of red corpuscles deprived of oxygen; (2) a bright red layer (sanguis) above this and formed by aërated red cells; (3) a grayish-white layer (mucus, phlegma) comprised of leukocytes and platelets; and (4) a yellow fluid, the blood serum (cholera). The phlegma, which was found so conspicuous in disease, not only attracted the attention of the Greeks, but of physicians for many centuries after the humoral theory had been discarded. Under such names as "crusta inflammatoria," "size" and "buffy coat," this gray layer was an index of disease even to Sydenham and to Bright. Venesection was performed in an attempt to rid the body of this noxious material.

As microscopic studies gained impetus, the macroscopic examina-

tion of the blood lost its vogue and, with the exception of hematocrit studies by Hedin,[2] Daland,[3] Herz,[4] Capps,[5] and a few others,[6] this method of blood examination was completely neglected. In 1918 Fahraeus[1] made his first observations on the suspension stability of the blood. His studies have aroused considerable interest. Working from another angle and chiefly stimulated by a paper by Haden,[7]

FIG. 1.—Hematocrit, pipette and bulb used for filling it, and cap for hematocrit. Two-thirds actual size. (Courtesy W. E. Prior Company, Inc.)

several students of the blood have again become interested in the determination of the volume of packed red cells by means of various types of hematocrit.[8] The macroscopic study of the blood as a whole has not, however, regained the position of importance it held for so many centuries.

The use of a hematocrit, previously described,[9] has in such a simple manner afforded so clear a macroscopic picture of the blood by its

employment not only for the measurement of volume of packed red cells but also for the determination of sedimentation rate, volume of packed white cells and platelets, and of icterus index, that the following description and discussion of these uses is presented.

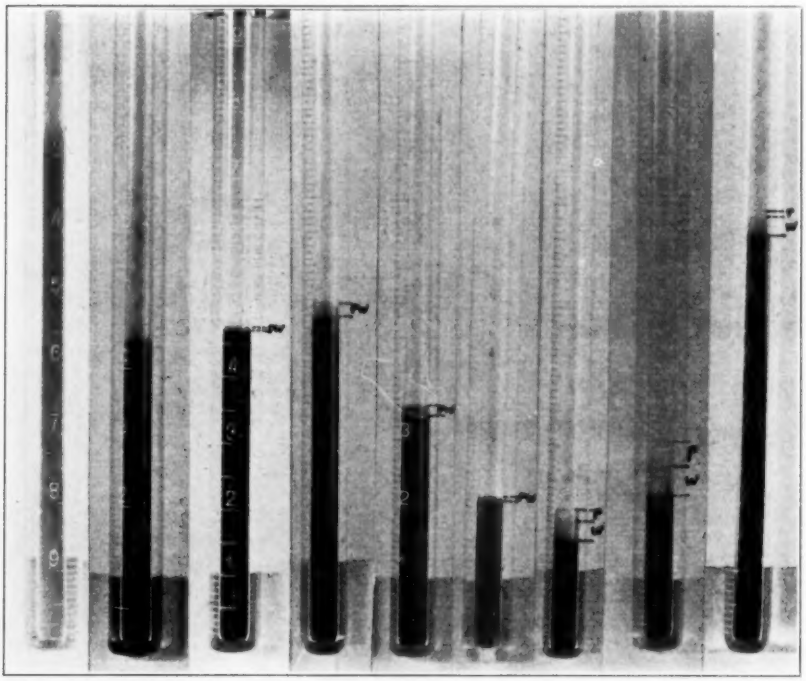

FIG. 2.—Appearance of the sedimenting red cells and of the corpuscular layers in the hematocrit. *A*, sedimentation of blood corpuscles, stage of rapid fall; *B*, sedimentation of blood corpuscles, stage of packing; *C*, normal blood; the reddish-gray layer is 0.5 mm. in thickness; *D*, no anemia; marked leukocytosis (W. B. C. 26,000); *E*, slight anemia; there is also slight leukocytosis; *F*, marked anemia; leukocyte count normal; *G*, case of myeloid leukemia, showing marked anemia, leukocytosis and thrombocytosis (R. B. C., 2.3 million; W. B. C., 35,000; platelets, 325,000); *H*, case of myeloid leukemia, showing less marked anemia (R. B. C., 3.6 million; W. B. C., 45,600; platelets, 430,000); *I*, case of polycythemia vera with leukocytosis and slight thrombocytosis (R. B. C., 6.7 million; W. B. C., 24,400; platelets, 430,000).

P = platelet (cream-colored) layer; *W* = leukocyte (reddish-gray) layer; *PW* = layer of platelets and leukocytes) corpuscles not separately distinguished). Hematocrits *C* to *I*, inclusive, were centrifugalized until no further packing occurred.

The hematocrit (Fig. 1)* is a narrow glass tube, somewhat less than 11 cm. long, with uniform bore (about 2.5 mm.) and flat inside bottom, on which a centimeter-millimeter scale 10 cm. in length is etched. Along the right side of the scale the numbers, 1, 2 . . . 10 are marked, commencing at the first centimeter mark above the bottom. At the left side of the scale

* The instrument may be obtained from Arthur H. Thomas Company, Philadelphia.

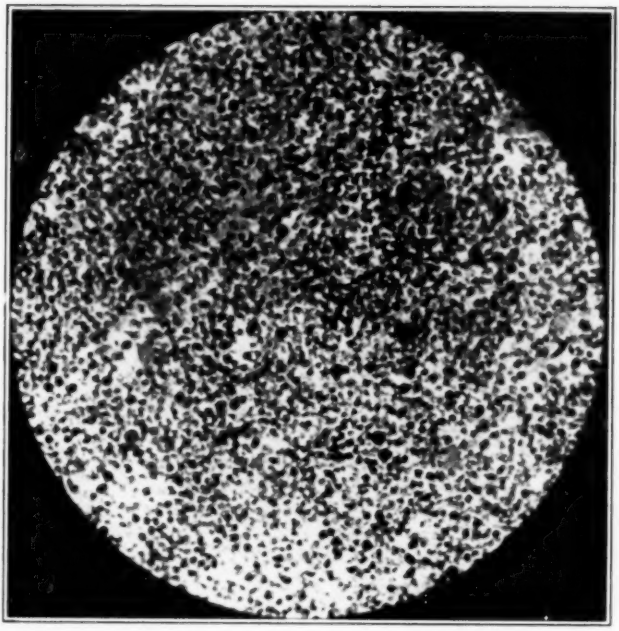

FIG. 3.—Microscopic view of the topmost, cream-colored layer of Fig. 2, *G*. Consists almost entirely of platelets. (× 500.)

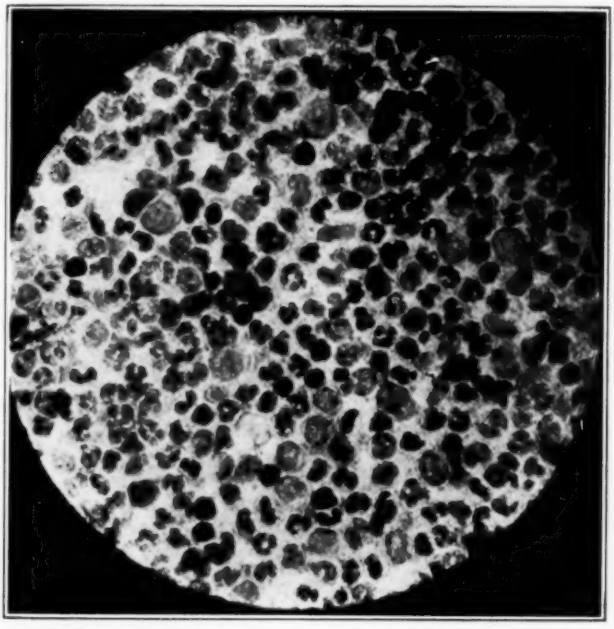

FIG. 4.—The reddish-gray layer below the cream-colored layer of Fig. 2, *G* (chronic myeloid leukemia). It is composed almost entirely of leukocytes. (× 500.)

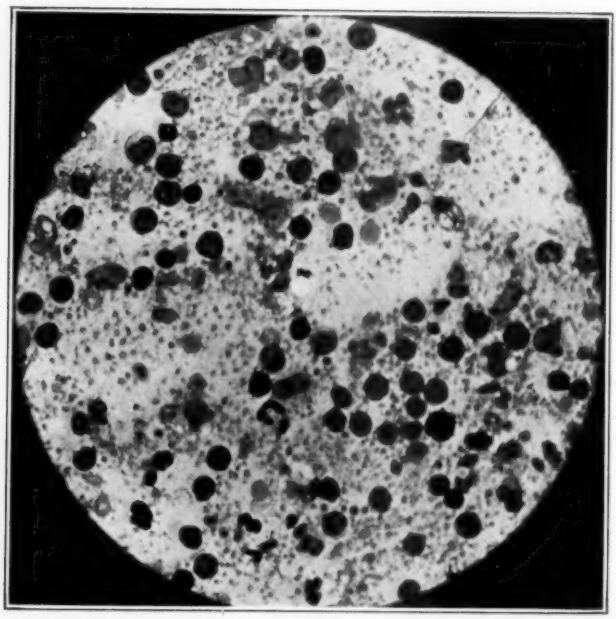

FIG. 5.—Microscopic view (×500) of material from the reddish-gray layer which was 1.1 mm. in thickness (leukocyte count, 10,050) of an infant's blood. There are many leukocytes, chiefly lymphocytes, and many platelets with scarcely any red corpuscles whatever.

the numbers 0, 1, 2 . . . 9 are found, these commencing at the upper portion of the hematocrit opposite the 10 mark. The figures at the right serve for volume readings, whereas those at the left are used for sedimentation readings.

Venous blood is obtained, care being taken to avoid congestion of the arm such as may be produced by prolonged application of the tourniquet. A clean, dry syringe and needle must be employed for drawing the blood. As anticoagulant dry potassium oxalate, 10 mg. per 5 cc. of blood, is used. In these quantities oxalate does not influence red cell, leukocyte, platelet or reticulocyte counts or the hemoglobin value, but a shrinkage in the volume of the red cells of 8.15 per cent takes place, which may be corrected by multiplying the volume of packed red cells, as read, by the factor 1.09. Our studies have shown that sedimentation-rate is not delayed by the use of this quantity of oxalate.

The chief objection which may be raised against the use of this hematocrit is that venepuncture is necessary. This is now so commonly done even for less important purposes that this disadvantage deserves little consideration. It is our general practice to collect 5 cc. of venous blood and a few blood smears (taken from the finger in the usual manner). Only 0.7 cc. of blood is required to fill the hematocrit, but by collecting 5 cc. a sufficient quantity is obtained at one time for any examinations desired and for repetition of counts which require checking. No quantitative alteration in any of the corpuscular elements occurs for at least 6 hours and usually for as long as 20 hours after withdrawal of the blood. It is important to employ a minimal and known amount of anticoagulant. Ten milligrams of potassium oxalate are most easily measured by running from a burette 0.5 cc. of a 2 per cent solution of potassium oxalate into a small bottle and allowing this to dry.

The hematocrit is easily filled by means of a capillary pipette, the narrow portion of which is of such a length that it can be passed to the bottom of the instrument. After the blood has been thoroughly mixed by inverting several times the corked vial or bottle* containing it, blood is drawn by means of a bulb into the pipette, and then, the pipette having been passed to the bottom of the hematocrit, the blood is gradually expelled as the pipette is withdrawn. This should be done so that no bubbles of air are formed in the hematocrit. The pipettes may be purchased but are easily made at a nominal cost. In order to prevent evaporation of plasma during centrifugation, the hematocrit is stoppered by means of a special cork. No special centrifuge attachment is required, the ordinary 15 mm. centrifuge metal holder being quite satisfactory. The hematocrit is easily cleaned by means of capillary pipettes similar to those employed for filling it. A very convenient arrangement is a syphon system consisting of three bottles containing water, alcohol and ether, respectively, to each of which a capillary pipette is connected. A continuous stream of water may thus be forced into the bottom of the hematocrit. After the instrument has been thoroughly cleaned it may be dried by passing alcohol and ether through it in a similar manner.

Determination of Sedimentation Rate. The test introduced to modern medicine by Fahraeus[1] is gaining increasing attention and appreciation as a nonspecific index of the presence and intensity of disease. The suspension stability (sedimentation rate) of the red blood corpuscles has been compared to fever and leukocytosis and

* We employ discarded liver-extract bottles of about 6 cc. capacity.

has been found to be more sensitive than either of these commonly used tests.[10] The sedimentation test is now employed in many clinics, particularly in the tuberculosis dispensary[11] and in gynecologic work.[12] Some observers think that it is of general value in detecting the presence of occult diseases of infectious and toxic origin.[13]

A variety of instruments has been employed for the determination of sedimentation rate. The presentation of another instrument therefore requires some justification because the multiplicity of techniques has already led to confusion. A disadvantage of the instruments commonly employed is that they can be used only for the determination of sedimentation rate. The employment of the hematocrit for this purpose is of special value because it has been demonstrated by several observers[14] that anemia magnifies and polycythemia minimizes the actual rate of sedimentation of the blood. If sedimentation is measured in a hematocrit, the volume of packed red cells may subsequently be determined without further trouble. In this way an accurate measure of the degree of anemia or polycythemia is obtained and an appropriate correction can be made. A correction chart which is applicable to the instrument here described is supplied by Rourke and Ernstene.[15]

The hematocrit is filled to the "10" or "0" mark. For the determination of sedimentation rate the fall in the upper level of red cells is measured in millimeters by the calibrations and the numbers at the left of the scale (Fig. 2, *A* and *B*). There is considerable debate whether the single observation of the distance which the red cells have fallen at the end of 1 hour is an adequate test of the suspension stability of the red corpuscles. The instrument here described is, however, suitable for the "time," "distance," or "graphic" procedures.[16] By means of an instrument devised in this laboratory,[17] the sedimentation of the red corpuscles may be photographically recorded.

Determination of Volume of Packed Red Corpuscles. After sedimentation rate has been studied, in order to determine the volume of packed red cells the hematocrit is centrifugalized until no further packing occurs.

The time necessary for this may be readily determined for any centrifuge by a few trials. When the International centrifuge, size 1, type SB, head radius 9 cm., is used at a speed of 3000 r. p. m., packing is complete usually in 20 minutes and always in 30 minutes. Complete packing is, of course, essential, as otherwise considerable error may be introduced. If the hematocrit has been filled to the "10" or "0" mark, the proportion of packed red cells may be read directly. If potassium oxalate has been used as the anticoagulant in the quantity specified, the volume of packed red cells, as read, must be multiplied by the factor 1.09 to correct for shrinkage. If heparin has been employed no correction is necessary.

The determination of volume of packed red cells by the method here described is accurate to within 0.5 per cent.[18] This probable error is less than that made in counting red cells even when the count is carefully carried out; and is much less than that of even the newer and more accurate methods of hemoglobin estimation.

The average volume of packed red cells for a large series of accurate determinations in healthy young men is 46 cc. per 100 cc. of blood, and in young women it is 41 cc. The variations for normal men and women are from 40 to 50 cc. and 37 to 45 cc., respectively. No large series of determinations has been made in older individuals, but the values which are available indicate that there is little or no change with advancing age as long as perfect health continues.[19]

Like either the red cell count or the hemoglobin value, the volume of packed red cells indicates the *degree of anemia or of polycythemia*. Neither the red cell count, the hemoglobin value or the volume of packed red cells is, however, alone a completely reliable index of the degree of anemia. As is well known, in certain types of anemia the red cell count may be normal when the hemoglobin and volume of packed red cells are even considerably reduced (microcytic anemias). In another type of anemia the red corpuscles are larger than normal and contain more than the normal amount of hemoglobin. In such cases the hemoglobin value and the volume of packed red cells may be normal when the red cell count is reduced. In pernicious anemia during a stage of incomplete remission such findings may be encountered. Again, although in the majority of anemias the amount of hemoglobin and the volume of packed red cells decrease or increase proportionately, in the hypochromic anemias the reduction in hemoglobin is even more marked than the decrease in the volume of packed red cells.

It is thus apparent that the volume of packed red cells is by itself no more certain an index of the degree of anemia, when all types are considered, than is the red cell count or the hemoglobin. Nevertheless, it may be considered equally important and, in view of the accuracy and ease with which it can be determined, in my opinion it *constitutes the most useful single criterion of the degree of anemia at present available.*

It has been the custom for many years to employ the red cell count and the hemoglobin as criteria of the *degree* of anemia, and the ratio between these, the color index, as a guide to the *type* of anemia. Many physicians have, however, lost faith in the color index because of the notorious inaccuracy of the commonly used methods of hemoglobin estimation and the great variety of standards employed as the equivalent of 100 per cent hemoglobin. The hematocrit fills an important gap in hematologic technique by making possible the calculation of the ratio between red cell count and volume of packed red cells, the information derived being essentially of the same significance and yet far more accurate than that afforded by the color index.[7] This ratio between red cell count and volume of packed red cells may be expressed in the form of the volume index[7] or the average volume of the red corpuscles may be calculated in absolute terms.[20] If the red cell count of the sample of blood used is known, the average volume of the red corpuscles (mean corpuscular volume) may be easily calculated by dividing the volume of

packed red cells, expressed in cubic centimeters per 1000 cc. of blood, by the red cell count, expressed in millions per cubic millimeter. The result gives the mean corpuscular volume in cubic microns. This method of expression is superior to the calculation of the volume index because, for the latter, certain standards of normality which must be arbitrarily fixed, are required.[20,21]

When it is possible to estimate the hemoglobin accurately it is very useful to calculate the mean hemoglobin content of the red corpuscles (mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) as well as their volume.[20] Such information is of great value not only in differentiating anemias but also in indicating the type of treatment that may be expected to be effective. This subject has, however, already been discussed in some detail elsewhere[21] and will, therefore, not be pursued here.

Determination of the Volume of Packed Leukocytes and Platelets. Another use of this hematocrit depends on the greater suspension stability of the leukocytes and platelets as compared with that of red corpuscles. When sedimentation is allowed to take place for an hour or longer in the hematocrit, the red cells become separated from the white corpuscles and platelets and, after centrifugation, the volume of packed leukocytes and platelets can be clearly distinguished from the volume of packed red cells.

In conditions in which the platelets and leukocytes are greatly increased in number, as in erythremia and sometimes in chronic myeloid leukemia, it is possible to secure by sedimentation and subsequent centrifugation a clear separation of all three corpuscles of the blood (Fig. 2, *G*, *H*, *I*). In such cases the platelets are found gathered together in a homogeneous cream-colored mass which constitutes the topmost layer (Fig. 2, *G*, *H*, *I*, and Fig. 3). The leukocytes form a homogeneous reddish-gray mass directly beneath the layer of platelets (Fig. 2, *G*, *H*, *I* and Fig. 4). Beneath the leukocytic layer is found the dark red layer of packed red corpuscles. The thickness of the layers of leukocytes and platelets may be taken as a rough measure of the quantity of these elements in the blood (Table 1*A*).

When the blood platelets are present in normal numbers they cannot usually be distinguished from the leukocytes. Under these circumstances only a reddish-gray layer is seen above the layer of packed red corpuscles. This reddish-gray layer (Fig. 2, *C*, *D*, *E*, *F*) is composed of both leukocytes and platelets (Fig. 5). In normal blood, when the hematocrit has been filled to the "10" mark, the reddish-gray layer is found to be 0.5 to 1 mm. in thickness (Fig. 2, *C*, *F*). That is, there is in normal blood 0.5 to 1 cc. of packed leukocytes and platelets per 100 cc. of blood.

When the platelet count is within normal limits the thickness of the reddish-gray layer corresponds very closely to the leukocyte count, each 0.1 cc. of reddish-gray material per 100 cc. of blood being equivalent to 1000 leukocytes per c.mm. The degree of accuracy

of this correlation is indicated by 103 observations recorded in Fig. 6. The correlation is greatest for counts up to 12,000, and is less exact for higher values. It may be noted, however, that in the majority of instances the correlation was sufficiently close to indicate leukocytosis when it was present and to give a rough index of its

TABLE 1.—VOLUME OF PACKED LEUKOCYTES AND PLATELETS.

*A. Leukocyte and Platelet Layers Distinguished.**

No. of observations.	W. B. C., average per c.mm. (thousands).	Volume packed W. B. C., cc. per 100 cc. blood.	Mean W. B. C. volume, c.μ.	Platelets, average per c.mm. (thousands).	Volume packed platelets, cc. per 100 cc. blood.	Mean platelet volume, c.μ.
3	16.1	1.6	990	547	1.7	31
3	23.0	3.2	1,390	860	1.1	13
5	34.8	3.0	810	870	2.6	30
5	44.2	2.9	660	567	3.2	56
3	54.3	2.9	540	1,040	2.4	23
1	60.7	4.6	760	1,080	2.5	23

* These observations were all made in cases in which the predominating leukocytes were granulocytes.

B. Cases in Which the Leukocyte and Platelet Layers Were Not Separately Distinguished.

Range of W. B. C. count (thousands).	Type of predominant cells.	No. of observations.	W. B. C., average per c.mm. (thousands).	Platelets, average per c.mm. (thousands).	Volume packed W. B. C. and platelets, cc. per 100 cc. blood.
1.0 to 5	Myeloid	17	3.6	256	0.36
5.1 to 10	"	40	7.6	236	0.73
10.1 to 15	"	26	12.0	177	1.25
15.1 to 20	"	9	17.0	195	1.39
20.1 to 30	"	7	23.6	330	2.32
30.1 to 40	"	2	33.1	250	4.0
40.1 to 50	"	1	50.0	140	3.2
60.1 to 70	"	1	69.3	....	7.5
Above 200	"	1	228.0	134	10.0
Above 200	"	1	316.0	135	8.0
Above 200	"	1	950.0	....	46.0
10.1 to 20	Lymphoid	3	17.0	215	0.77
40.1 to 50	"	1	40.7	282	1.1
410 to 500	"	2	417.0	30	11.4
510 to 600	"	4	551.0	181	11.1
610 to 700	"	4	689.0	139	15.1

degree. As may be seen by examining Table 1, *B*, when the leukocyte count was excessively high, 0.1 cc. of packed leukocytes and platelets corresponded more nearly to 2000 leukocytes per c.mm. Furthermore, it is evident that when the predominating cells are lymphocytes, the factor given is incorrect, 0.1 cc. of reddish-gray layer corresponding in such instances approximately to 2000 leukocytes per c.mm. when the total count is relatively low (25,000), and to 4000 or 5000 cells when the count is high (40,000 or higher).

These observations are not recorded here with any object of presenting an easy method of determining the leukocyte or platelet count. The avenue of progress in hematology is in the direction of greater accuracy rather than in that of ready but rough procedures.

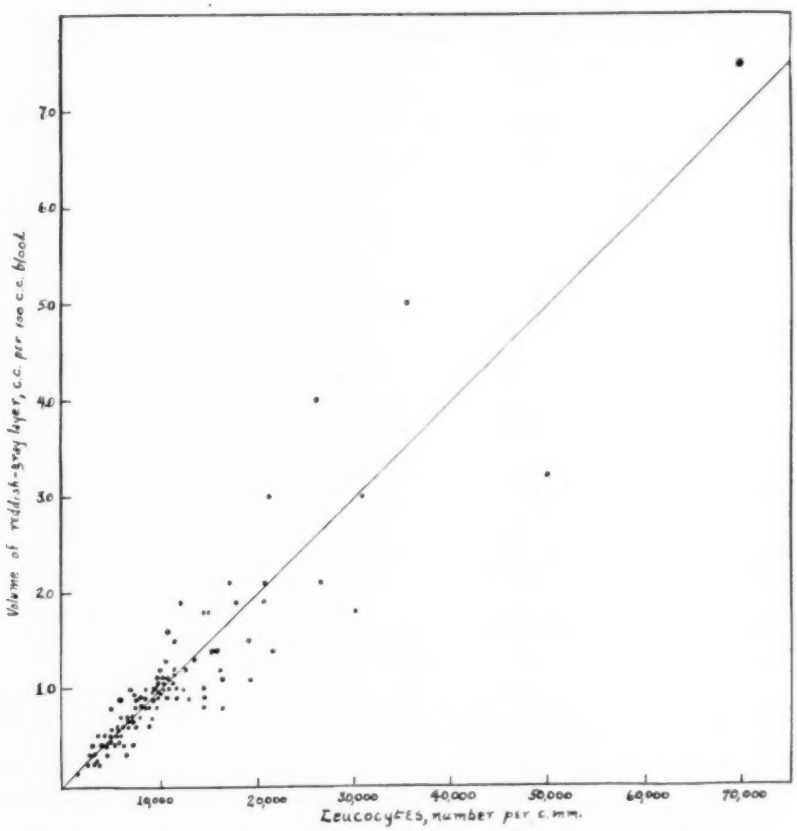

FIG. 6.—Correlation of volume of reddish-gray layer, consisting of packed leukocytes and platelets, to leukocyte count. Only those cases in which the predominating leukocytes were of the myeloid series and in which the platelet count was within normal limits, are included: 103 observations. The coefficient of correlation for the 100 observations in which the leukocyte count was 30,000 per c.mm. or less is 0.8582 ± 0.0178.

Nevertheless, the thickness of the layer of packed leukocytes and platelets may serve, in the hands of experienced workers, as a useful rough guide to the quantity of these corpuscles in the blood. Thus, an extremely thin reddish-gray layer suggests leukopenia or, if the leukocytes are known to be present in normal numbers, it suggests thrombocytopenia. Again, when the layer above the packed red corpuscles is creamy in color rather than reddish-gray and yet not abnormally thick, one may suspect thrombocytosis and leukopenia.

On the other hand, as already mentioned, a thickened reddish-gray layer indicates leukocytosis, and from the thickness of this layer a fairly accurate estimate of its degree can be made.

If, in addition to the volume of packed leukocytes and of packed platelets, the number of leukocytes and platelets is known, it is possible to calculate their mean volume by a method similar to that followed in calculating mean corpuscular volume.[20] Our data show the average volume of the cells of the myeloid or granulocytic series to be 800 c.μ with the cells ranging between 500 and 1500 c.μ in size. In chronic lymphoid leukemia the lymphoid cells were found to vary between 170 and 300 c.μ. The mean volume of the platelets has ranged from 13 to 50 c.μ and averaged 30 c.μ (Table 1, A). At the present time this information is, however, of academic interest only.

Determination of Icterus Index. The measurement of icterus index has come into general use since the work of Meulengracht[22] and of Bernheim.[23] It is now well known that, in the absence of liver disease, biliary obstruction and carotinemia, an increase in the yellow color of the blood serum or plasma is generally due to the presence of increased quantities of bilirubin resulting from increased blood destruction. Significant differences in the degree of bilirubinemia occur in the various types of anemia. Very commonly, however, in the cases of anemia in which hyperbilirubinemia occurs, this is not sufficiently great to be readily detected by physical examination alone. On the other hand, physical findings may be misleading for the pallor of the skin may be so great that it appears yellowish even when there is hypobilirubinemia. Such findings are not uncommon in chronic posthemorrhagic and in hookworm anemia. The estimation of icterus index is therefore of particular value in hematologic studies.[24]

The measurement of the degree of icterus of the supernatant plasma in the hematocrit is the next obvious step in the use of this instrument. This has proved to be a most useful adjunct to the study of the blood.

For this purpose a comparator box* (Fig. 7) has been devised which holds a series of sealed tubes similar to the hematocrit as regards thickness of glass and inside bore. These tubes contain potassium dichromate solution in such dilutions as correspond to the icterus index units suggested by Murphy[25] and now generally employed. For the determination of icterus index, the hematocrit is placed, after centrifugation, in a special compartment in the comparator box and the comparator tubes are placed one on each side of it. A window permits only the upper, plasma-filled portion of the hematocrit to be seen. The comparator tubes are interchanged until one is found which matches the color of the blood plasma. The unit value is marked on each tube. It is particularly important when icterus index is to be determined that all apparatus used be clean and dry and that the blood be drawn before meals or some time after the taking of food, as otherwise lipemia may make the color matching difficult or impossible.

* Made by Arthur H. Thomas Company, Philadelphia.

Icterus index determinations by this method have been compared with values obtained by other techniques and have been found accurate. Blood serum is usually employed for the determination of icterus index by other methods, but we have found no differences between the icterus index values of serum and plasma.

The normal range of icterus index is usually considered to be 4 to 6 units. Values lower than 4 units indicate decreased blood destruction and are consistently encountered in chronic post-hemorrhagic and simple achlorhydric (hypochromic microcytic) anemia and, less frequently, in aplastic anemia and the simple microcytic anemia associated with chronic infections and intoxications. We usually hesitate to consider values of 7 or 7.5 units

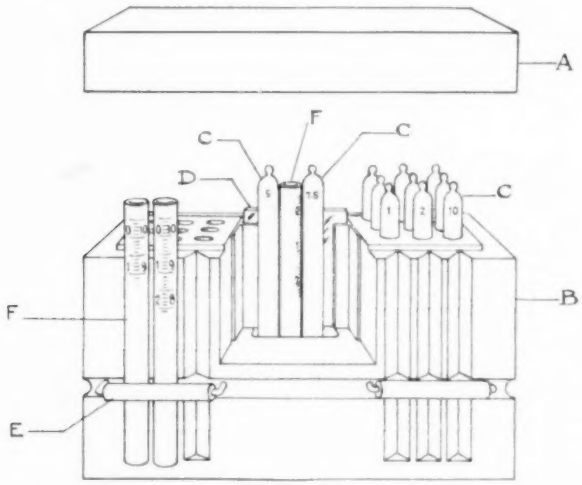

FIG. 7.—Icterus index comparator box and sedimentation rack. *A*, lid for box; *C*, icterus index standard tubes; *D*, blue glass; *E*, spring catch which holds hematocrits in position during sedimentation; *F*, hematocrit.

as significantly increased. Distinctly high values are characteristically found in sickle-cell anemia and in anemias caused by hemolytic agents such as malaria. In differentiating hemolytic from nonhemolytic types of anemia, the icterus index test is very valuable. In pernicious anemia the icterus index is characteristically greater than normal and is frequently high even when there is little or no anemia. In the latter instances hyperbilirubinemia and slightly increased mean corpuscular volume[21] may be the only abnormal findings in the blood examination.

In interpreting the results of icterus-index determinations it must always be borne in mind that liver disease (even chronic passive congestion), obstruction of the biliary passages and increases in the lipochromes (lutein, carotin, and so on) of the blood, as occur following the ingestion of large quantities of eggs, oranges and chlorophyll-containing vegetables, cause an increase in the yellow color

of the blood plasma. It is very unusual for vegetables or eggs unless ingested in excessive quantities to influence the blood of adults but the ingestion of carrots, even as few as two, has been found to have a distinct effect on the blood.[23]

When the icterus index test is employed in hematologic studies it must particularly be borne in mind that the absorption of blood from ecchymoses and hematomata such as are frequently encountered in the purpuras, both idiopathic and secondary (acute leukemia, aplastic anemia, etc.), may in itself lead to hyperbilirubinemia.

The Value of Examining the Appearance of Blood Plasma. As additional evidence of the value of gaining a macroscopic view of the blood may be cited two recent experiences. The first occurred in the course of our routine complete blood study in a case of Addison's disease. The plasma was found to be exceptionally cloudy, much more so than we had encountered in instances of post-prandial lipemia. Blood drawn again before breakfast revealed the same milky plasma. This accidental observation led to chemical studies which resulted in the discovery of chemical abnormalities in this patient's blood which had not previously been suspected.

A most unusual experience occurred in connection with a patient who complained of nosebleed, oozing of blood from the mouth, coldness, discoloration and pain in the extremities, and pain and swelling of the right shoulder joint. Physical examination made the diagnosis no less obscure. Blood examination, undertaken on account of the bleeding, revealed the presence in the hematocrit of cloudy plasma and a yellowish-gray layer 10 mm. in height above the layer of packed red cells. The finding of this gray layer which somewhat resembled the gray layer formed by leukocytes, was most surprising for it was already known that the leukocyte count and the platelet count were reduced rather than increased. Microscopic examination of the yellowish-gray material showed that it was made up of droplets of a brownish viscid substance which, on drying, crystallized. Furthermore, it was observed that the cloudy material in the plasma appeared on cooling and disappeared at room temperature. This variation with temperature put one in mind of the action of Bence-Jones protein and, in view of the associated anemia, leukopenia and thrombocytopenia a diagnosis of bone-marrow tumor was suggested. Subsequent examination and autopsy confirmed this suggestion. A detailed account of the observations in this case will be given elsewhere.[26]

Summary. By a series of consecutive steps which are simple and may be quickly performed, it is possible by the use of a single instrument, a modified hematocrit, to gain accurate and valuable information concerning the blood.

1. Five cubic centimeters of blood are drawn from a vein with a dry syringe and needle and placed in a small bottle containing 10 mg. of potassium oxalate with which the blood is thoroughly mixed.

2. The hematocrit is filled to the "10" mark by means of a capil-

lary pipette and *sedimentation rate* is determined. The sedimentation rate serves as a guide to the presence and intensity of organic destructive or infectious disease.

3. The filled hematocrit is next centrifugalized until no further packing of the corpuscles takes place. The *volume of packed red corpuscles*, and the *volume of packed leukocytes and platelets* may then be read.

The volume of packed red cells is an accurate index of the degree of anemia and is more easily and more accurately measured than even the red cell count. It also serves to correct the sedimentation rate of the blood, as above determined, for the influence of anemia or polycythemia. Furthermore, if the red cell count and hemoglobin value of the sample of blood collected for hematocrit studies has been determined, the mean volume and hemoglobin content of the red corpuscles may be calculated. The latter information is of great value not only in differentiating the anemias but also in serving as a guide to the type of treatment which may be expected to be effective.

The volume of packed white cells and platelets serves as a rough guide to the quantity of these corpuscles in the blood.

4. Finally, the *icterus index* of the plasma may be read and this, in the absence of liver disease, biliary obstruction and carotinemia, serves as a useful guide to the degree of blood destruction.

Conclusion. The use of the hematocrit in the manner described affords, at the expense of very little time and effort, so clear and comprehensive and yet so accurate a macroscopic picture of the state of the blood, that its employment may well be considered in routine diagnostic studies. This method of employing the hematocrit is not recommended as a substitute for more detailed microscopic or chemical studies but, in experienced hands, it can be made to indicate along what lines the further study of the blood should proceed. This may well be the first blood study in those diagnostic clinics in which the technical personnel is too limited to permit the routine performance of erythrocyte, leukocyte and platelet counts as well as hemoglobin and van den Bergh tests.

My own experience with the hematocrit has convinced me that of the three instruments, the hemocytometer, the hemoglobinometer and the hematocrit, the last named affords more information concerning the blood than either of the other two, and indeed the information is more accurate. It is now my practice to use it in all diagnostic blood studies.

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BILATERAL CORTICAL NECROSIS OF THE KIDNEYS (ANGIONEUROTIC ANURIA).

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(From the Army Medical Museum. Publication authorized by the Surgeon-General, U. S. Army.)

This strange pathologic entity has been the concern chiefly of the obstetrician, but the accumulation of at least 18 incidences where it has occurred in association with conditions entirely unrelated to pregnancy makes it the concern also of the internist. It is now obvious that Carson and Rockwood's[1] conclusion, written in 1926, that bilateral (symmetrical) cortical necrosis is invariably associated with pregnancy is no longer tenable, for the pathology is identical with the pregnant and the nonpregnant groups.

If the incidence of the condition be based solely on the pathologic anatomy, it will include only those patients who have died and whose kidneys show the orthodox picture of diffuse necrosis of the cortices. I accept the angioneurotic theory of the pathogenesis, however, and can assume that there is variation in the severity of the

vascular reaction. There are disturbances sufficiently severe to interfere with renal function but adjustable before the tissue is irreparably damaged. For the purposes of this paper, I have not gone so far as to include all the cases of nonobstructive anuria, but, as Scriver and Oertel[2] have done in their recent paper, I have accepted a number of cases with typical clinical pictures, but with deficient pathologic data. Bilateral cortical necrosis becomes a pathologic term under these conditions and indicates the terminal lesion. I suggest angioneurotic anuria as a clinical term applicable to all cases of nonobstructive anuria.

Scriver and Oertel's[2] excellent article includes references to 37 cases from the literature and 3 cases of their own. This is the largest collection to date. With the advantage of ready access to the Surgeon's-General Library, however, I have increased the number of reported cases to 60 and am adding 2 from my own experience.

In the attempt to discover heretofore unrecognized cases and to establish priority for the description of the condition, the following articles on eclampsia were reviewed: Leyden,[3] the first to speak of the "kidney of pregnancy," King,[4] Bouffe de St. Blaise,[5] Schmorl,[6] Lubarsch,[7] Wienberger,[8] Dürck,[9] Petersen,[10] Edebohls,[11] Franck,[12] Zinsser,[13] Zangemeister,[14] Goldzieher,[15] Fahr,[16] v. Fekete *et al.*,[17] Hinselmann,[18] v. Jashke,[19] Zondek,[20] Fahr[21] and Zangemeister's[22] recent monograph. These articles include over 400 cases. In addition to these, 70 cases of anuria as reported by Cerou,[23] Merklen,[24] Neubürger[25] and Falci[26] were reviewed. It is probable that some of these were cortical necrosis, but none has been included in the series. One of Schmorl's[6] cases, a woman, aged 35 years, who died with a clinical diagnosis of eclampsia, is particularly suggestive. He found infarcts of hyalin material in the capillaries and glomeruli, tubular thrombi in the arterioles and fat emboli in some of the glomeruli. He speaks of infarction, but he is not clear as to the distribution of the necrosis and he gives no clinical data. Lubarsch,[7] Weinberger,[8] Dürck[9] and Peterson[10] also describe fat emboli in the glomeruli, more or less thrombosis in the smaller vessels of the kidney cortex and the epithelium as varying from normal to completely necrotic. These data are suggestive, but are not sufficient to establish the cases as authentic. Kellogg,[27] in his study of the kidneys in cases with premature separation of the placenta, includes a group of 5 which showed partial or complete anuria. Only 1 of them was given in sufficient detail to warrant its inclusion, although the other 4 may have been equally acceptable.

The credit for the first recognizable pathologic description remains with Juhel-Rénoy.[28] There was a lapse of 12 years, however, before the lesion was established as a definite entity by Bradford and Lawrence's[29] case report.

TABLE I.—SUMMARY OF 42 AUTHENTIC CASES OF BILATERAL CORTICAL NECROSIS ARRANGED CHRONOLOGICALLY.

TABLE 1.—SUMMARY OF 42 AUTHENTIC CASES OF BILATERAL CORTICAL NECROSIS ARRANGED CHRONOLOGICALLY.

Author ref. No.	Sex.	Age.	Basic clinical data.	Convulsions	Headache.	Emesis.	Renal pain	Impaired vision.	Sys. blood pressure.	Edema.	Coma or drowsiness	Number, days of anuria. Partial	Number, days of anuria. Complete	Albuminuria	Nitrogen retention.	Remarks.
28	F	16	Scarlatina	+	..	+	+	..	..	+	..	6	6	..	..	None.
29	F	36	Preg. VI	–	..	..	..	..	Low	–	+	7	Almost	..	..	Normal pregnancy; drowsy, weak, postpartum.
52	F	30	Preg. V	+	..	+	..	..	..	..	–	10	Almost	..	..	Abdominal pain; convulsions day of death.
38	F	39	Preg. VII	+	+	+	..	+	188	..	–	11	Almost	..	..	Oliguria antepartum; hemorrhage.
53	F	35	Preg. V	–	+	+	..	+	140	+	–	11	6	..	..	Chronic nephritis; hemorrhage.
45	F	25	Preg. I	+	..	..	..	..	..	+	+	13	Almost	+	..	Cesarean; stupor just before death.
59	F	36	Eclampsia VII	+	+	..	..	..	..	+	+	5½	Almost	..	..	Convulsions; decapsulation, right.
59	F	22	Preg. 8 m.	+	+	+	..	+	..	+	+	8	6	..	..	Eclampsia; extremities cold and livid (Raynaud's ?).
56	F	29	Preg. 4 m. IV	–	–	+	..	..	Low	+	–	8	Almost	..	..	Edema slight; "pulse low tension."
42	F	38	Preg. 7 m. IX	–	..	..	..	..	..	+	–	4½	4½	..	..	Hemorrhage; dyspnea; urinous odor.
42	F	38	Preg. II	+	..	+	..	..	..	+	+	2½	Almost	..	..	Live twins.
42	F	23	Preg. 4½ m. I	+	+	+	..	+	..	+	+	7	2	..	..	Eclampsia; hiccough; hematemesis.
37	F	23	Preg. 7 m. I	+	..	..	..	..	280	..	+	1½	1½	..	..	Eclampsia; hemorrhage; decapsulation, bilateral.
57	F	48	Preg. XIII	–	..	+	..	..	115	–	..	8	8	..	..	Macerated fetus; abdominal pain; dyspnea.
47	F	22	Preg. I	+	+	+	..	..	..	+	+	3½	Almost	+	..	Eclampsia; premature.
48	F	35	Preg.	+	..	..	..	..	..	..	+	4½	4½	..	..	Eclampsia? fits antepartum; coma postpartum.
46	F	38	Preg. 7 m. III	–	..	+	..	..	150	..	..	4½	4½	..	..	Renal tenderness.
58	F	29	Preg. 8 m. I	–	+	..	+	+	..	+	+	8	Almost	+	..	Hemorrhage; renal tenderness; decapsulation.
50	F	14	Camphor	..	..	..	..	..	..	..	+	4	4	+	..	Camphor benzol, intrav., q. 2 h.; anuria 48 h. later.
50	..	..	Camphor	..	..	..	..	..	..	..	..	..	..	..	..	Benèke's case; cortical necrosis at necropsy.
42	F	48	Preg. VII	+	..	..	..	..	..	+	+	5½	5½	..	..	Toxemia; bilateral decapsulation.
49	M	46	Diphtheria	..	..	..	+	..	..	..	..	7	7	..	..	Suspected renal calculus.
38	M	37	Malaria	..	+	+	..	..	..	..	+	2	Almost	..	..	Spleen tender; dysenteric symptoms.
62	F	33	Preg. 5 m. X	..	+	+	+	..	145	..	..	9	5	..	..	Old nephritis; abdominal pain; hemorrhage.
46	F	38	Preg. II	+	..	..	..	+	..	+	..	7	5	..	..	Eclampsia; Cheyne-Stokes breathing last day.
21	M	65	Ca. prostate	..	..	..	..	..	..	..	..	..	..	..	..	No clinical data; pathology cortical necrosis.
30	F	30	Preg. II	+	+	+	..	+	120	..	..	9	Almost	..	+	Normal until fourth day postpartum; decapsulation.
1	F	36	Preg. 6 m. VI	–	..	+	..	+	200	..	+	6	Almost	+	..	Macerated fetus.
51	F	22	Rupture liver	–	..	..	..	..	..	..	+	2½	Almost	+	..	Hemorrhage and shock.
41	F	38	Preg. 8 m. I	–	..	..	..	..	150	..	..	12	0	+	+	Abdominal pain; shock; hemorrhage; Cesarean.
63	F	..	Preg.	..	..	..	..	..	..	..	..	6	Almost	..	..	Original reference not obtained.
40	F	29	Preg. 8½ m. I	..	..	+	..	+	..	+	..	5	1	+	+	Glycosuria; decapsulation; recovery.
64	F	34	Preg. 6 m. XV	–	..	–	..	..	170	–	..	9	9	+	+	Hemorrhage.
39	F	29	Preg. II	..	..	..	..	..	170	+	..	8	Almost	+	+	Detached placenta; macerated fetus.
36	M	13	Tuberculosis	..	..	+	..	..	..	+	..	..	..	+	+	Diarrhea and abdominal pain.
34	F	37	Preg. 7 m. IV	–	..	+	..	+	118	+	+	12	Almost	+	..	Hemorrhage; macerated fetus; uremic odor.
34	F	39	Preg. 7 m. III	–	..	..	+	..	120	+	..	12	Almost	+	..	Macerated fetus; dyspnea.
34	F	24	Preg. 6½ m. III	..	+	+	..	+	..	+	..	..	..	..	..	Abdominal pain; Cesarean.
34	F	33	Preg. IV	..	+	+	..	+	117	+	–	20	6	..	+	Premature; abdominal pain; decapsulation.
32	F	30	Placenta prev. I	–	..	+	..	..	150	+	+	11	11	+	+	Hyperemesis; Cesarean.
2	F	38	Preg. 6 m. VIII	–	..	..	..	..	160	–	+	5	5	+	+	Hemorrhage; anuria 2 days postpartum.
55	F	38	Preg. VIII	+	+	..	..	+	..	+	–	2½	2½	..	..	Cesarean; decapsulation, right.

TABLE 2.—SUMMARY OF 18 PROBABLE CASES OF BILATERAL CORTICAL NECROSIS.

Author ref. No.	Sex.	Age.	Basic clinical data.	Convulsions.	Headache.	Emesis.	Renal pain.	Impaired vision.	Sys. blood pressure.	Edema.	Coma or drowsiness.	Number, days anuria. Partial.	Complete.	Albuminuria.	Nitrogen retention.	Remarks.
54	F	13	Rheumatic heart	..	..	..	..	..	..	..	..	..	..	..	..	No clinical data; path. suggestive.
54	M	69	Ca. prostate	..	..	..	..	..	180	+	–	8½	8½	..	..	Mentally clear; nephrotomy, right.
65	F	22	Hemiplegia	+	..	..	..	..	..	..	+	..	..	+	+	Anemia; sudden onset; suggestive pathology.
37	F	31	Preg. V	..	..	+	..	+	..	+	..	2½	1	+	..	Separation of placenta; Cesarean; no pathology.
44	F	38	Preg. I	..	..	..	..	..	..	..	..	4	1½	..	..	Separation of placenta; *recovered;* no pathology.
33	F	..	Eclampsia I	+	..	..	..	..	160	+	+	9	0	..	..	Cesarean; decapsulation, rt; *recovered;* biopsy.
33	F	..	Preg. 6 m. II	+	..	..	..	..	..	+	+	17	0	+	..	Labor induced; nephrotomy; *recovered;* biopsy.
47	M	64	Lobar pneumonia	–	..	..	..	..	..	..	..	4	0	+	..	Pathology suggestive.
47	F	10	Peritonitis	..	..	+	..	..	..	..	..	..	..	..	..	Abd. pain; laparotomy; pathology suggestive.
43	M	52	Renal colic	..	..	..	+	..	..	..	..	4	4	..	..	Decapsulation, lt.; anuria, rt., 14 days; *recovered.*
66	M	13	Polyarteritis	+	–	–	..	..	..	–	..	7	0	+	..	Abdominal pain; fever.
21	M	4	Dysentery	..	..	..	..	..	..	..	..	..	..	..	..	No clinical notes; pathology very suggestive.
21	M	56	Arteriosclerosis	+	..	..	..	..	..	..	..	..	..	..	..	Pathology suggestive.
31	F	25	Preg. III	+	..	..	+	..	..	..	..	13	13	+	+	Onset 6 days after delivery; nephrotomy, lt.; died.
60	F	43	Crushed chest	..	..	..	..	..	..	..	..	..	..	..	..	Died twenty-second day; rt. kidney necrotic.
27	F	40	Preg. 6 m.	..	..	+	..	+	160	+	..	6	2	..	+	Separation of placenta; Cesarean; *recovered.*
39	F	22	Eclampsia I	..	+	..	..	+	220	+	+	3?	..	+	..	Living child; pathology suggests eclampsia.
2	F	37	Preg. 4 m. IV	..	..	+	+	..	100	+	–	7	0	..	+	Hyperemesis; hemorrhage; fluids forces; *recovered.*

In selecting the cases from the literature effort has been to avoid padding and some cases that were probably authentic were rejected arbitrarily, so that the collection may be regarded as a conservative representation. The pertinent data are given in Tables 1 and 2, the latter being a segregation of those cases to which exception might be taken.

My 2 cases are of particular importance because they were both males, apparently healthy until the sudden onset of the renal symptoms, and both presented kidney pathology as typically bilateral cortical necrosis as that seen in the pregnant women with eclamptic symptoms. Unfortunately, the clinical data are meager.

Case Abstracts. CASE 1.—A white soldier, aged 25 years, in good health, was seized suddenly with severe pain in the lower abdomen, nausea and vomiting on December 11, 1928. On admission to the hospital the same day his temperature was 102.2° F., his pulse 74 and respirations 20. It was suspected that he was suffering from acute appendicitis. He was given an enema, and food by mouth was stopped. The abdominal pain ceased on the second day in hospital, but he continued to vomit. Anuria became apparent at this time and the bladder was found empty on catheterization. A small quantity of urine obtained later contained albumin, hyalin casts and red blood cells. The vomiting persisted and increased in severity until his death, on December 29. For the last 2 days he had a constant diarrhea, and on the last day he developed air hunger and collapsed. There was no noteworthy change in his mentality nor did he have any convulsions. His blood pressure was 120 systolic and 85 diastolic after the onset, but no other readings were recorded. No estimation of urine secretion was made, but there was more or less complete anuria from December 12 to December 29, an unusually long period of 17 days. No blood chemistry determinations were made.

Pathologic Anatomy. The body was fairly well nourished and well developed. There was a punctate papular rash over the hands and feet, but no edema. The organs were considered normal except the kidneys. These were slightly enlarged and flabby, and the capsules stripped readily. Only formalin fixed tissues were received for examination, so that the details of the gross appearance were obscured. (Fig. 1.) In the broadened cortex, however, can be recognized the opaque, yellowish-white zone of necrosis with loss of normal markings and small, irregular, dark spots of hemorrhage. This necrosis extends almost to the capsular surface and to within a few millimeters of the pyramids, but it does not involve the columns of Bertini. It is defined from the more normal cortical tissue by a dark border of congestion. The pyramids stand out in contrast to the pale, turbid cortex, because of the dark streakings of their engorged vessels. None of the bloodvessels large enough to be seen grossly shows thrombosis or evidence of sclerosis.

Microscopic Appearance. The architecture and distribution of the lesion are well shown in the low power picture in Fig. 3. With higher magnifications, the following details are seen in the left kidney: In the narrow subcapsular zone the tubules are intact, although some of them are moderately dilated, and their epithelium is degenerated, usually hydropic. Some of the lumina contain desquamated cells, hyalin and necrotic débris and a few polymorphic leukocytes. These are not convoluted tubules, and the impression is that the material in them has come up from the necrotic zone. There are no intact glomeruli in this zone, nor is there any interstitial exudate to speak of. The bloodvessels are congested with

healthy red blood cells. This zone is interrupted by broad and narrow extensions of the completely necrotic zone to the surface of the kidney, and the inner limit is irregular from the projection into it of necrotic glomeruli and convoluted tubules.

There is a sharp transition into the zone of necrosis. Here there is scarcely a healthy cell to be seen, although the architecture can still be identified. There is considerable exudate, both interstitial and intratubular in the outer portions, but it also is necrotic and is present chiefly as pyknotic bodies and nuclear fragments. The epithelium of some of the convoluted tubules lying close to the larger intralobular* arteries takes the basic stain, indicating calcium deposit.

In the more central portions of this zone are large areas in which there is scarcely any evidence of a nucleus, and this only scattered fragments in the interstitial tissue. A hazy picture, in which the elements can scarcely be distinguished, except that the convoluted tubules stand out fairly prominently because their swollen, necrotic cells have taken the acid stain more deeply. The exudate increases again at the inner border of the necrotic zone. Some of the necrotic glomeruli and tubules project into the suprapyramidal zone and mingle with live elements, but there is no transition zone of partially necrotic structures.

The vessels in the necrotic zone are uniformly engorged and their walls necrotic, some disintegrated and invaded by leukocytes. Special staining shows the elastica in some of the vessels toward the periphery to be practically intact, in others disrupted or entirely absent. The intralobular arteries stand out prominently because of the layer of thrombus laid down on the intima, as shown in Figs. 5 and 6. This layer varies in thickness, but in no instance is the lumen entirely occluded. Phosphotungstic acid hematoxylin stain shows these thrombi to be composed of fused and hyalinized fibrin augmented by enmeshed conglutinated red cells, but no platelets can be recognized, nor is there any evidence of organization. The red blood cells in the remaining lumina of these intralobular arteries are usually discrete and well stained, but there is some conglutination in the larger masses. The tubular thrombi extend into many of the afferent arteries and end as plugs at the glomeruli. This is shown in Fig. 6. There is practically no thrombosis of the glomerular capillaries, except for the occasional extension of the thrombus in the afferent artery into a glomerular lobule. The red blood cells in the glomeruli and in the efferent arteries are usually discrete though pale, and they stain poorly with phosphotungstic acid hematoxylin. They are evidently older than those proximal to the thrombi. The smaller interstitial vessels are engorged but not thrombosed, and there are no thrombi outside the necrotic zone. There are large arteries at the inner border of this zone that are not thrombosed, although their walls are necrotic. Small, recent hemorrhages, some of which are from ruptured glomeruli, others from leakage through the necrosed walls of bloodvessels, are scattered through the center of the necrotic zone.

In the suprapyramidal cortex there is some apparently recent increase in the interstitial connective tissue adjacent to the necrotic zone. There is a moderate generally distributed interstitial edema, and a small amount of exudate. The bloodvessels are congested and some of them contain bacterial masses. These are agonal and of no etiologic significance, for they are seen also in the vessels of the spleen, liver and pancreas without any reaction referable to their presence. Several of the glomeruli are engorged with healthy blood, but otherwise they are normal. The epithelium of the tubules is well preserved, but there are many casts and considerable débris in the tube lumina.

* Gross's terminology is used. Intralobular arteries are the interlobular, and the interlobar are the arcuate arteries of the older terminology.

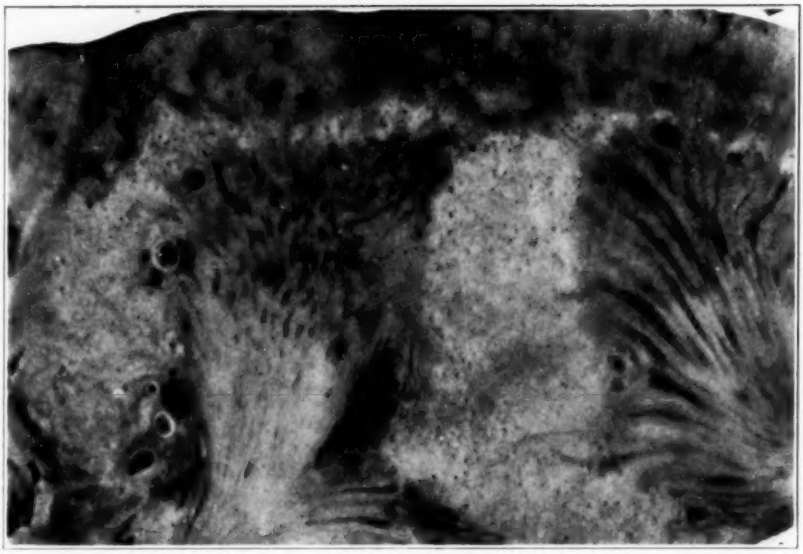

FIG. 1.—(Case 1.) Cortex necrotic and mottled with hemorrhages; thrombosis of intralobular arteries; columns of Bertini and suprapyramidal zones comparatively uninvolved; medulla congested; large vessels patent. A. M. M. Neg. 49423. ($\times 1\frac{1}{4}$.)

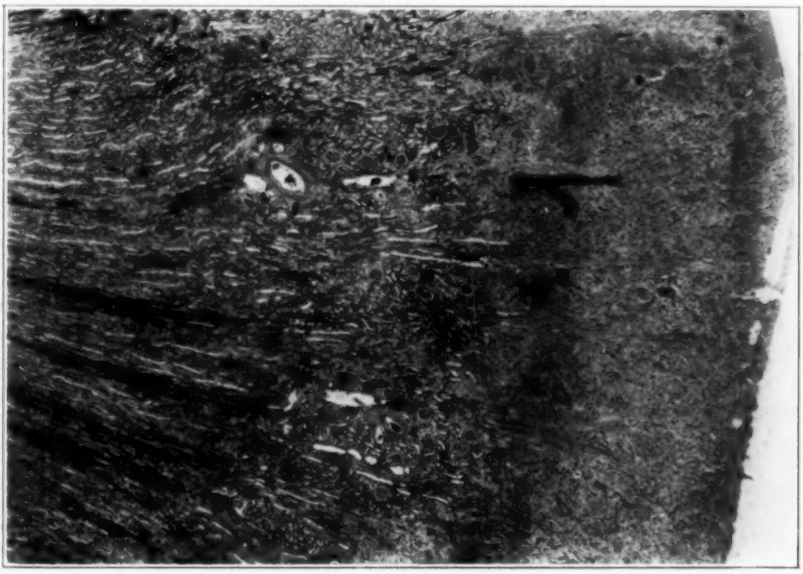

FIG. 2.—(Case 2.) Necrotic zone of cortex outlined by shaded zone of congestion and exudate in which intralobular arteries are thrombosed. Medulla congested. A. M. M. Neg. 49410. ($\times 9$.)

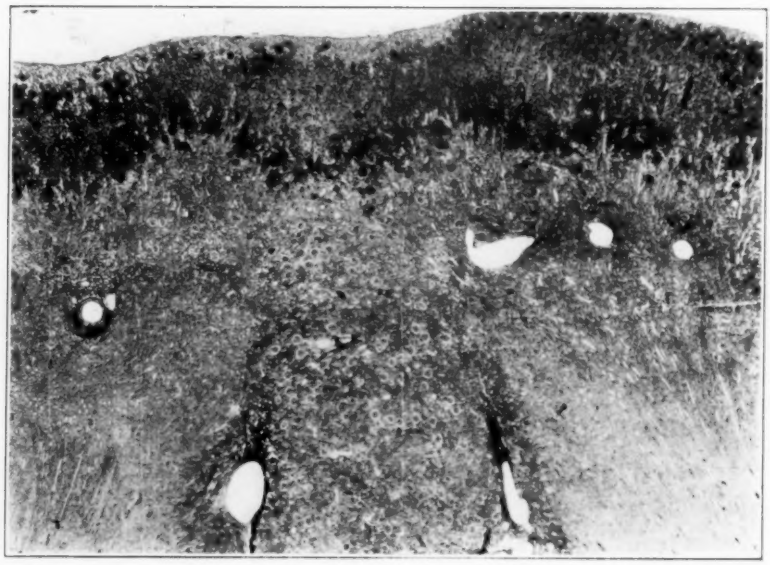

FIG. 3.—Section of kidney from Case 1 stained with phosphotungstic acid hemotoxylin, which emphasizes the zone of congestion and exudate and the thrombi. The non-necrotic subcapsular zone can be recognized readily. A. M. M. Neg. 49442. (× 8.)

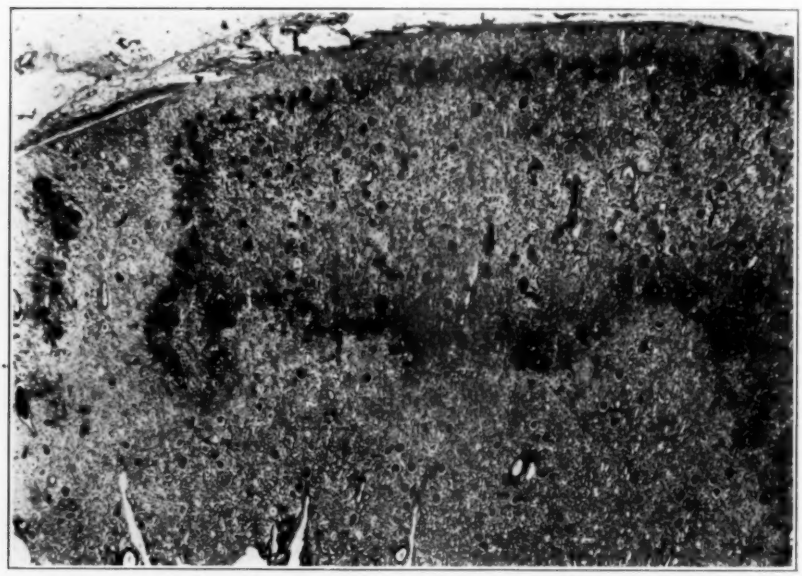

FIG. 4.—(Case 2.) Kidney from Case 2. Same stain as Fig. 3. A comparatively free strip of cortex extends to the capsular surface. The free subcapsular zone is broader than that in Fig. 3. A. M. M. Neg. 49446. (× 9.)

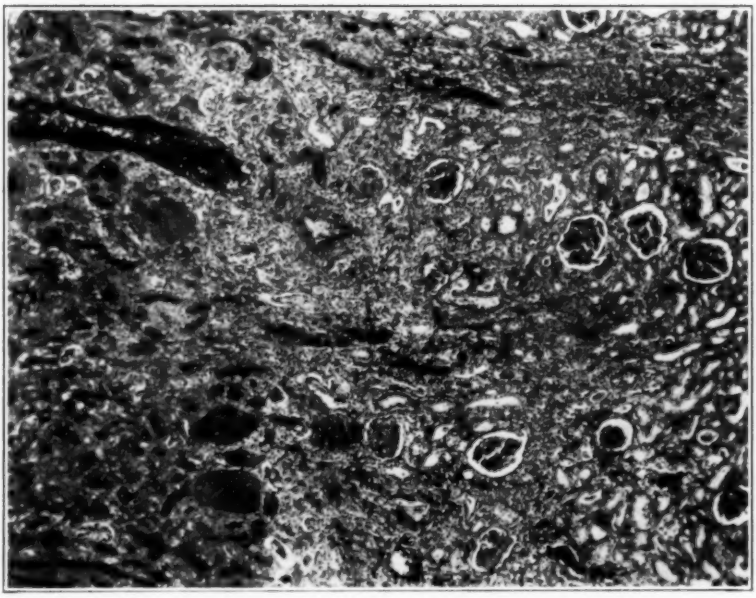

FIG. 5.—(Case 1.) Suprapyramidal free zone to the right; zone of complete necrosis to the left; intervening zone of exudate and irregular necrosis. A widely dilated and necrotic intralobular artery contains a tubular thrombus. A. M. M. Neg. 49413. (× 45.)

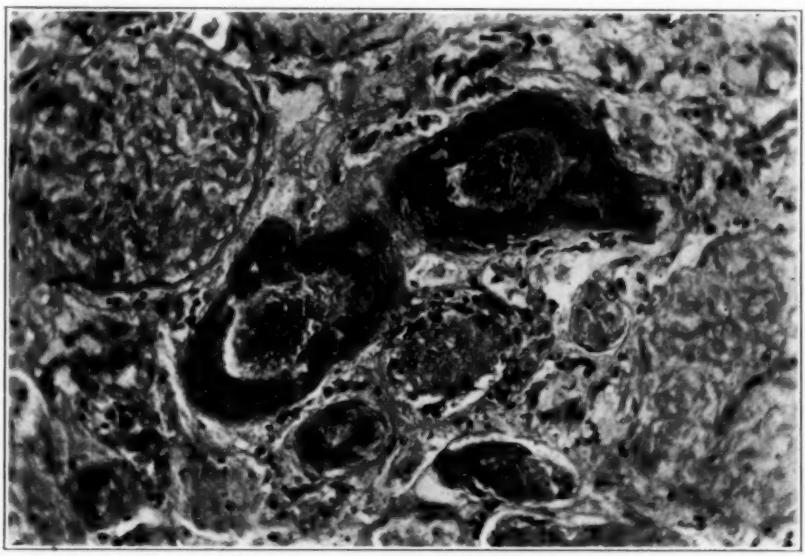

FIG. 6.—(Case 1.) From the necrotic zone near the subcapsular area. Tubular thrombi in necrosed intralobular arteries. Glomeruli engorged but not thrombosed. Some of the nuclear fragments may represent old exudate. Interstitial edema. A. M. M. Neg. 49415. (× 200.)

FIG. 7.—(Case 2.) Thrombosis of afferent arteriole; glomerular capillaries distended with partially laked red cells. Necrosis of all structures with preservation of architecture and absence of exudate. A. M. M. Neg. 49406. (× 310.)

The large collecting tubules of the pyramids are filled with casts, exudate or necrotic débris, although their epithelium shows little change. Some of the epithelium of Henle's loops is swollen and granular, but generally it is not much altered. The lumina usually contain more or less granular and hyalin débris. The vessels are engorged, but the walls show no damage. There is some interstitial edema, and extending up from the pelvic mucosa are broad streaks of chronic exudate consisting of polymorphic leukocytes, lymphocytes, a few plasma cells and eosinophils. Similar exudate is found in the pelvic fat. Beneath the pelvic mucosa there is some hemorrhage, and the exudate contains a larger proportion of polymorphic leukocytes. The large vessels at the hilus do not show any noteworthy change. The distention of the interlobar vessels can be seen in Figs. 2 and 3.

The right kidney presents a similar picture, except that there is more exudate in the prenecrotic zone, but fewer hemorrhages and less thrombosis. The thrombi do not show the tubular arrangement so strikingly.

In addition to the bacterial masses in the vessels of the spleen, pancreas and liver, the latter contains a few fat droplets in the cells of the central zones, and the pancreas is the seat of postmortem change.

Case 2.—A white army officer, aged 32 years, who likewise gave no previous indication of anything wrong, was seized with nausea and vomiting on July 22, 1928. He was admitted to the hospital, July 24, complaining of pain over the entire abdomen and extreme tenderness over both kidneys. The following day he complained of inability to void. He was catheterized and 10 cc. of "thick" urine containing albumin, and hyalin and granular casts were obtained. There was almost complete anuria for the first week, and during the following 12 days until his death, August 12, he passed from 120 to 150 cc. of dark urine per day. Each specimen contained albumin and casts. His temperature for the first 2 days in the hospital was 99.5° to 100° F., following which it was normal or subnormal. The nausea and vomiting were persistent, but he had no convulsions nor mental disturbance. There is no record of the blood pressure nor of blood chemistry determinations.

Pathologic Anatomy. (Autopsy limited to abdomen.) The body was well developed; there was no superficial edema. The peritoneal cavity contained 1 liter of straw-colored fluid. The kidneys were both enlarged, tense and their capsules stripped readily. In this case also were received only pieces of the kidneys that had been fixed in formalin. The distribution of the necrosis, however, can be seen in Fig. 4. The subcapsular zone is broader than that in Case 1, but the necrotic zone is also deeper and it involves the columns of Bertini. In this case there are strips of nonnecrotic cortex extending from the pyramids to the capsular surface, interrupting the necrotic zone. The large vessels are free.

A piece of small intestine was the only other tissue received, and it shows a moderate hyperemia with some postmortem desquamation of its epithelium. Except for minor variations, the kidneys present the same picture as do those of Case 1. The necrosis was even more sharply defined and more extensive. The necrotic zone looks as though it were unfixed tissue that had been in water for a long time. There is less thrombosis of the larger vessels, although the plugging of the afferent arteries at the glomeruli is as frequent.

Clinical Summary. Symptoms. The important symptoms are summarized in Tables 2 and 3. This can be done only approximately, and no percentage estimation of the occurrence of the various symptoms is possible, because of the meagerness of data in the majority of the case reports. It cannot be assumed that a symptom was absent simply because it was not noted.

One is impressed by the comparatively mild clinical picture, especially in those cases not complicated by eclampsia nor by the toxemia of pregnancy. In several incidences the symptoms improved decidedly after the uterus had been emptied, in spite of the anuria. There was a distinctly lower incidence of convulsions, headache and edema than one sees in uremia, and there was much less mental disturbance. A number of the patients were perfectly clear mentally until a few hours before death. The picture is much the same as that resulting from obstruction of both ureters, or from bilateral nephrectomy.

Anuria, partial or complete, is the only symptom common to all the cases. It may appear without any premonitory symptoms of kidney damage, or it may follow a normal pregnancy with uneventful delivery, as illustrated by the cases reported by Bradford and Lawrence,[29] Hirst[30] and Iungano.[31] It varies in duration and degree from 1 day of complete suppression to several weeks of diminished flow. In the majority of cases the duration has been 8 days or less. Iungano's[31] patient apparently holds the record with 13 days of complete anuria, with Dalrymple's[32] case second with 11 days. There have been several instances of partial suppression for longer periods, however. One of White's[33] patients recovered after 17 days; Case 4 of Davidson and Turner[34] lived 20 days, during 6 of which anuria was complete, and both of my patients survived for unusually long periods, 15 and 19 days, respectively.

Diarrhea was a noteworthy symptom in several cases, sufficiently severe in Bamforth's[35] to suggest dysentery. Apert and Bach[36] speak of it particularly in their boy with tuberculosis, and it was a terminal symptom in my first case. It may have represented an attempt at compensatory elimination of fluids.

Blood pressure is mentioned in 23 cases, in 14 of which it is well within normal limits. The highest is reported by Couvelaire,[37] a pressure of 280 mm. Hg in a primipara with eclamptic symptoms in addition to the anuria. In 3 instances of high pressure there was a reduction following the emptying of the uterus. In Lloyd's[38] case it dropped from 188 to 120; in Carson and Rockwood's,[1] from 200 systolic and 130 diastolic to 170 systolic and 110 diastolic; in Westman's[39] second case, from 200 systolic and 150 diastolic to 130 systolic. The high readings were all recorded in pregnancy complicated by eclampsia or placental hemorrhage. Apparently the anuria *per se* did not affect the blood pressure materially.

A definite *nitrogen retention* is reported in 12 cases. As might be expected, it was greatest in the eclamptics. Crook's[40] case showed a total blood nonprotein nitrogen of 388 that returned to normal after kidney decapsulation. The highest blood creatinin was reported by Manley and Kliman,[41] 12.5. As may be seen in Table 3, the 5 records of creatinin are all high. Scriver and Oertel[2] call attention to this rapid accumulation in cortical necrosis, and

contrast it to the slower rise seen in chronic nephritis and in chronic urinary obstruction, as from carcinoma of the prostate.

TABLE 3.—BLOOD CHEMICAL FINDINGS IN 10 CASES OF BILATERAL CORTICAL NECROSIS.

Author.	Nonprotein nitrogen, mg.	Urea nitrogen, mg.	Creatinin, mg.
Kellogg	100		
Hirst		106	7.0
Manley and Kliman		75	12.5
Crook		388*	
Westman		71	
Apert and Bach		290	
Dalrymple	300		
Scriver and Oertel		..	6.6
Scriver and Oertel		..	6.4
Scriver and Oertel	104*	..	6.0

* Returning to normal.

Urine. The 22 cases in which urinalyses were recorded showed albumin; the majority of the specimens contained casts and 5 of them blood.

DIFFERENTIAL DIAGNOSIS. This depends almost entirely on the interpretation of the anuria. The latter may be a feature of several other conditions, especially nephritis, hysteria, poisons and general dyscrasias, but renal infarction and bilateral ureteral occlusion are the two important conditions which must be excluded before making the diagnosis of bilateral cortical necrosis. As has already been mentioned, the clinical picture presented by cortical necrosis resembles closely that seen in obstructive anuria, particularly in the mildness or absence of uremic symptoms. The differentiation, of course, depends on a careful urologic examination to determine the patency of the urinary tract.

The differentiation of cortical necrosis from renal infarction may not be so easy. Sudden onset, nonradiating renal pain, albuminuria, hematuria and oliguria are common to both. But, while renal pain was mentioned in only 11 cases of cortical necrosis, it is a constant and prominent symptom in renal infarction of sufficient extent to interfere with urinary output. Anuria, on the other hand, is not so constant a feature of infarction, nor is it so likely to be complete as it is in cortical necrosis. Infarction is usually an accident of cardiovascular disease, so that the history of the patient and a general physical examination are important.

Jardine and Kennedy[42] think that it is impossible to differentiate cortical necrosis from chronic nephritis complicating pregnancy.

PROGNOSIS AND TREATMENT. In its strictly pathologic sense bilateral cortical necrosis must be considered invariably fatal. So much of the essential tissue is destroyed that the process is equivalent to a bilateral nephrectomy. There is no evidence that the necrosis is ever sufficiently limited to leave enough functioning parenchyma to sustain life, as is the case in infarction.

If, however, we use the term in its broader sense, accepting the vasomotor theory of pathogenesis, we may include cases that recover. There are 7 of these in the 62 cases of this series. They did not have the pathological entity of bilateral cortical necrosis. In White's[33] 2 cases, and Crook's[40] single case, all of which recovered, the biopsy specimens did not show the necrotic stage of the condition, and we must conclude with White, that the necrosis is the terminal stage of the process.

There seems to be no way, however, of determining clinically in what stage of the pathologic process a given case may be, for the symptoms were just as severe in the patients who recovered as in those who died. We can assume that those who recovered did not have extensive necrosis, but we cannot say with assurance that any treatment they received prevented its development. In several instances, however, there was evidence of a favorable influence from treatment, and I cannot agree with those who believe that all treatment is hopeless. Pal's[43] experience is particularly significant. After decapsulation of the *left* kidney of a man who had had a complete anuria for 4 days the daily urinary output increased to 1800 cc., but the *right* kidney remained anuric for 2 weeks. Crook's[40] patient, who had been anuric over 4 days, passed 33 ounces of urine during the day following the decapsulation of her right kidney, and she eventually recovered. Experiences of this sort are of greater significance in evaluating the influence of treatment than the fact that only 4 recovered of the 13 patients on whom decapsulation or nephrotomy was performed; for the pathologic examination of those who died showed that necrosis had already developed at the time of the operation. Edebohls,[11] who first suggested the operation of decapsulation, in 1904, reported the recovery of 3 cases of oliguria in eclampsia following his operation, and Franck,[12] in 1907, collected 10 cases of which 6 recovered. It is with the hope, therefore, of possibly aborting the process in the prenecrotic stage that operation is advocated. White[33] recommends as a routine procedure the splitting of the kidney capsules during a Cesarean section on eclamptics with oliguria.

On the other hand, the 3 additional recoveries in my collection reported by Kellogg,[27] Scriver and Oertel[2] and Oldfield and Hann,[44] had no kidney operation, but were treated with glucose and the forcing of fluids. Kellogg[27] is a particular advocate of this form of treatment on the theory that the maintenance of a high blood pressure favors reëstablishment of the circulation through the engorged renal vessels. He particularly condemns decapsulation.

Dalrymple,[32] assuming that the process results from toxins, advocates the plasmapheresis of Irving and Taylor.

Pathologic Anatomy. There is a noteworthy uniformity in the lesions of the kidneys in the authentic cases. The variations are minor ones, often depending on differences in interpretation. The

picture resembles roughly that of an anemic infarct, except for the peculiar distribution, less extensive hemorrhage and strikingly greater engorgement of the vessels in the necrotic areas. Hemorrhages and exudate have been mentioned by several authors, but they are not constant. Calcium deposit in the necrotic cells as seen in my first case is mentioned by Klotz,[45] Geipel,[46] Iungano[31] and Scriver and Oertel.[2] The last two observers also found large quantities of fat, not only in the necrotic cells, in which it is common, but in the tubular and vascular lumina, a unique feature in this series of cases. But the chief variation is in the discussion of the thrombi, their composition, point of origin and distribution. While the reports are practically unanimous in limiting them to the necrotic zone, Herzog[47] and Schüppel,[48] for example, believe that they begin in the glomeruli or afferent arteries and extend centrally, while Geipel[46] and Westman[39] believe they originate in the larger cortical vessels and extend peripherally. Several of the authors confirm the finding in my 2 cases of the frequency of occluding plugs in the afferent arteries at their entrance into the glomeruli. Stöckenius[49] speaks of it particularly. The majority, also, have noted the scarcity of thrombi distal to the afferent arteries. The thrombi have been described as being composed of blood platelets, fibrin, conglutinated red blood cells and combinations of these. While these discussions are interesting, one is forced to conclude that the thrombosis is, after all, not the cause of the lesion, but that it is a secondary feature. In 14 of the 44 authentic cases thrombi were either not mentioned or they were too few and scattered to have been the primary cause of such extensive necrosis.

There is one interesting and important feature of the pathology that must be emphasized. The duration of the anuria seems to make little difference in the terminal picture. The same degree of necrosis and thrombosis is described in those cases which have died after a few days of anuria as is seen in those which have lived 8 or 10 days. Zanzig,*[50] for example, describes extensively necrotic cortices with all of the cortical vessels filled with thrombi in the kidneys of a girl, aged 14 years, who died after 4 days of anuria following camphor injections.

Furtwängler[51] describes practically complete cortical necrosis that must have developed within 60 hours after an automobile accident, in which the liver was ruptured but in which the kidneys were not directly injured. It is true that organization and fibrosis have been mentioned in a few instances. Zaaijer[52] describes granulation tissue in the kidneys from his patient who died after 10 days of

* This author has been referred to as "Zunzig" by several writers, the last, in 1927. His Dissertation, unfortunately, is not indexed in the Index Medicus, the Cumulative Index or the Catalogue of the Surgeon-General's Library. It was only after considerable search, therefore, that the original was located in the Surgeon-General's Library.

almost complete anuria, and Griffith and Herringham[53] found an increase of the interstitial tissue in their case who died after 11 days of anuria, but this fibrosis was very likely an evidence of the chronic nephritis for which she had been under treatment for some years. But it does seem that if the thrombosis and necrosis were responsible for the anuria, there would have been more evidence of an attempt at organization and repair than has been reported in the 22 cases in which the anuria lasted for 8 days longer

ETIOLOGY. From the clinical data presented, it will be seen that of the 44 authentic cases, 34 complicated pregnancy, 2 followed the intravenous use of camphor, 3 were of cryptogenic origin and 1 occurred in each of the following conditions: scarlet fever, diphtheria, carcinoma of prostate, pulmonary tuberculosis and trauma. Of the 18 cases about which there may be some question, 8 were in pregnancy, and 1 each in dysentery, carcinoma of the prostate, rheumatic fever, anemia, lobar pneumonia, polyarteritis nodosa, arteriosclerosis, acute peritonitis, trauma and 1 was of cryptogenic origin.

Seven of the 62 patients were children, the youngest a boy, 4 years (Fahr[21]), and the oldest a girl, aged 16 years (Juhel-Rénoy[28]). The oldest patient of the series was Weber's,[54] a man, aged 69 years, with carcinoma of the prostate. Of the 20 which did not occur in pregnancy 7 were females and 12 were males. The sex of 1 was not stated. The only significant feature of the distribution in age and sex is that the 4 cryptogenic cases were adult males.

These 4 cases are of particular interest, for they establish the fact that cortical necrosis can develop in the absence of obvious disease.

In only 2 cases was trauma involved, but that it is a more important factor than these 2 selected cases would indicate is evidenced by Cerou's[23] Merklen's[24] and Neubürger's[25] reports of anuria lasting from 18 hours to 14 days, only 1 of the patients surviving.

There are 42 instances of cortical necrosis occurring in pregnancy. Twelve of them were primiparas and 27 multiparas of from 2 to 15 para. In 3 cases the number of pregnancies was not recorded. Twenty-one of the patients were over 35 years of age, the oldest being 48 years, and 12 were under 30 years, 3 of these being but 22 years. There is, therefore, a higher incidence in multiparas over 35 years of age.

In only 7 patients did the cortical necrosis occur at full term, and only 4 were delivered of living children. These last cases were reported by Jardine and Kennedy[42] (twins), Immink,[55] Westman[39] and Iungano.[31] In 7 instances it was stated that the fetus was macerated.

In only 11 cases was the pregnancy uneventful before the onset of the anuria. Of the others, 20 had had uncomplicated edema, 17 evidence of renal damage and 9 had been diagnosed eclampsia.

Spontaneous abortions, induced labors, Cesarean sections are frequently mentioned in the reports. Scriver and Oertel[2] attach significance to the fact that there was retroplacental hemorrhage in 13 cases.

That the anuria may be a delayed phenomenon is evidenced by Iungano's[31] case in whom it did not occur until 13 days after a normal delivery, by Hirst's[30] with a delay of 4 days and by Jardine and Kennedy's[42] in whom it developed several days after a therapeutic abortion.

In order to explain the uniform picture seen in the kidneys from this series of cases, it must be assumed that there is some factor or combination of factors that are common to at least the many clinical conditions cited above. It is obvious, also, that either this factor is more commonly present in pregnancy than in any other clinical condition, or pregnancy affects the kidneys in some way to make them more sensitive to it. It is not surprising, therefore, that so much of the discussion in the literature is concerned with pregnancy, and that every real and hypothetical condition incident to pregnancy has its advocates as an etiologic factor. But while increased coagulability of the blood, alterations in blood pressure, specific toxins originating in the placenta (the dead fetus or otherwise) and affecting the vascular endothelium or the renal epithelium, ischemia from pressure, emboli originating in placenta, liver or from the fatty tissues may be factors determining the relatively high incidence of cortical necrosis in pregnancy, they cannot be accepted as immediate instigators of the process. At present there are not enough data to indicate just what does cause the condition.

Pathogenesis. With the cause unknown, there must be, also, divergence of opinions as to the mechanism producing the lesions. The extent and distribution of the necrosis eliminate emboli as the first step in the process. Juhel-Rénoy[28] was the only advocate of this theory. Zaaijer[52] thought that increased intrarenal pressure could compress the less resistant afferent arteries sufficiently to cause necrosis of the large portion of the cortex which they supplied. Pal[43] and White[33] advance a somewhat similar hypothesis. Weber,[54] Hirst,[30] Manley and Kilman,[41] Bamforth[35] and Kennedy[42] look upon the epithelial damage as primary and the thrombosis secondary. Crook[40] suggests that interference with metabolism and with water elimination, probably through disturbed pituitary influence, may affect the kidneys sufficiently to cause the necrosis.

The other authors can be divided roughly into two schools. Bradford and Lawrence,[29] Lloyd,[38] Griffith and Herringham,[53] Klotz,[45] Torrens,[56] Rolleston,[57] Herzog,[47] Schüppel,[48] Geipel,[46] Glynn and Briggs,[58] Stöckenius,[49] Carson and Rockwood,[1] Westman,[39] Davidson and Turner[34] and Dalrymple,[32] all regard the process as primarily a thrombosis, attributing it variously to toxic damage

of the vascular endothelium, qualitative blood changes that increase the coagulability, altered intrarenal blood pressure or a combination of these factors.

Jardine and Teacher,[59] Zanzig,[50] Furtwängler,[51] Immink,[55] Fahr,[21] v. Marenholtz[60] and Kellogg[27] belong to the other school which holds that the first step is a spasm of cortical vessels. It is interesting to note that Cerou,[23] writing in 1877, and Merklen,[24] in 1881, explain the anuria following trauma and burns as the result of reflex vasoconstriction, basing this opinion on Claude Bernard's and Bulpin's investigations of the reflex nerve influence on the vascular supply of the kidneys and on urinary secretion. Neubürger[25] explains the gross infarcts which he found after trauma as due to the spastic closure of branches of the renal arteries, the result of strong mechanical irritation, and Zangemeister[22] ascribes the lesions of eclampsia to focal angiospasm. In Scriver and Oertel's[2] recent article Oertel discusses convincingly the vasomotor origin of the phenomenon. Basing his interpretation of the lesion largely on the studies of Ricker[61] on the response of vascular elements to various degrees of irritation, he considers it after all "the results of irritations of arterial terminal segments of different intensities." In the terminology of Ricker, the zone of dilated arterioles and capillaries and of exudate represents "peristasis," the zone of vasoparesis and hemorrhage represents "prestasis" and the necrotic zone with complete cessation of blood flow is the final stage of vessel collapse "stasis." Oertel tends to emphasize the vasostasis, and it certainly is a striking feature of the picture, but he acknowledges the possibility that the primary reaction to the "irritant" may be vasoconstriction.

The experiments of Cohnheim, Lubarsch, Litten and others have shown that an ischemia of about 2 hours' duration is sufficient to produce necrobiosis in the kidney, and that this time is materially shortened if the ischemia is complicated by a toxemia. Perhaps this toxemia is furnished by pregnancy or the other clinical conditions, including the shock of trauma. These conditions may contribute also to the formation of the thrombi. The evidence indicates that the thrombosis is secondary, not to the necrosis, as some would claim, but to the stasis. The thrombi begin in the afferent arteries and extend in a proximal direction to the limit of the necrosis, so that they rarely go beyond the interlobar arteries. They are rare in the glomeruli, efferent arteries and veins. The blood in these vessels is "stale" and so may have lost some of its coagulability. The exudate does not indicate a primary inflammatory reaction as much as it does the reaction to necrotic tissue.

Summary and Conclusions. 1. Sixty-two cases of bilateral cortical necrosis of the kidneys selected from the literature and 2 added from personal experience have been analyzed.

2. The condition occurs most commonly in pregnancy, but is seen also in a variety of infectious diseases; it may follow trauma and it may develop cryptogenically. The pathology and pathogenesis are the same under any of these conditions.

3. Bilateral cortical necrosis is a pathologic term applicable only to the terminal stage of certain cases of nonobstructive anuria. It is recommended that "angioneurotic anuria," therefore, be adopted as a clinical term to include all nonobstructive anurias.

4. Treatment is of no avail in the pathologic condition "bilateral cortical necrosis," but there is evidence that decapsulation of the kidneys or nephrotomy will favorably influence an otherwise refractory angioneurotic anuria.

5. The immediate cause or causes of bilateral cortical necrosis are not known, but in my opinion it is most probable that the anuria is the result of vasomotor disturbance, probably a vasoconstriction that is followed by vasoparalysis and stasis, and that the striking picture of necrosis and thrombosis found postmortem is relatively terminal. Depending on conditions which are not understood, these terminal lesions may develop after a few hours of anuria, may be deferred for days or may not develop at all. In the last circumstance the patient may recover.

NOTE.—I wish to express my gratitude to Prof. Howard T. Karsner and his assistants at the Pathologic Institute of Western Reserve University, Cleveland, for assistance in identifying the lesions in Case 1, to Dr. Neuman and Mr. Toepper, Assistant Librarians at the Surgeon-General's Library, for their generous aid in tracing ambiguous references, and to Major Paul E. McNabb, Curator of the Army Medical Museum, for seeing the manuscript through the press during my absence on foreign service.

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THE SIGNIFICANCE OF THE LARGE Q WAVE IN LEAD III.

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That the *Q* wave in Lead III may become large in coronary occlusion was noticed by Pardee[1] and later by Parkinson and Bedford[2] and Levine.[3] Pardee[4] lately offered criteria for defining the large *Q* wave in Lead III and called attention to the fact that the majority of such records are obtained from patients with the anginal syndrome. Willius,[5] in reviewing his records, finds that this abnormality in the electrocardiogram is by no means limited to the anginal syndrome, but seems to occur in diseases exerting their influence chiefly on the left ventricle. Fenichel and Kugel[6] recently studied the correlation of such electrocardiograms with pathologic findings and concluded that the large *Q*–3 is the most frequent electrocardiographic finding of coronary artery disease during the chronic stage, and that the large *Q*–3 in myocardial infarction and fibrosis is probably due to the involvement of the posterior portion of the septum. These observations stimulated us to investigate the electrocardiographic tracings in our files.

Material. The files in the electrocardiographic laboratory contain tracings not only of patients from the Cardiac Clinic, but of patients from other clinics as well. A number of these patients have no organic heart disease, hence our records represent not only a variety of cardiac patients, but also a fair number of normals.

Seventy-five of the 2000 electrocardiograms carefully studied were found to conform with the qualifications set forth by Pardee,[4] namely: (1) In Lead III a downward initial deflection (*Q*), succeeded by a definite upward deflection (*R*), with no (*S*) following. (2) An excursion of the *Q* wave in Lead III of more than 25 per cent of the greatest excursion of the *Q*–*R*–*S* complex in any lead (Fig.1). (3) Elimination of electrocardiograms with right axis deviation as *Q*–3 is a normal finding in such records. (4) Exclusion of records with notching deformity of the *Q*–*R*–*S* complex in any lead, the so-called *W* and *M* complexes.

Clinical Correlation. The correlation of the electrocardiograms under discussion with the clinical diagnosis is given in Table 1. The greatest incidence of the characteristic electrocardiograms occurred in cases of hypertension, that is, of the 75 electrocardiograms with the large *Q*–3, 25 (33.3 per cent) were obtained in cases of this type. The anginal syndrome occurred only in 12 cases (16

per cent), luetic aortitis in 9 cases (12 per cent) and arteriosclerosis in 8 cases (10.5 per cent).

TABLE 1.—CORRELATION OF LARGE *Q* WAVES IN LEAD III WITH CLINICAL CONDITION IN 75 CASES.

Clinical diagnosis.	Cases.	Per cent.
Diseases affecting chiefly the left ventricle:		
Hypertensive heart disease	25	33.33
Anginal syndrome	12	16.00
Luetic aortitis	9	12.00
Arteriosclerosis	8	10.50
Total	54	72.00
Miscellaneous:		
Rheumatic heart disease	12	16.00
Postthyroidectomy	1	1.30
Cretinism	1	1.30
Auricular fibrillation (cause unknown)	1	1.30
Emphysema	1	1.30
Pregnancy (record after delivery did not show large *Q*–3)	1	1.30
Effort syndrome	1	1.30
Congenital heart	1	1.30
Apparently normal hearts	2	2.20
Total	21	28.00

Analysis of Results. Our results differ from those of Pardee,[4] and those of Willius[5] in some respects, but agree fairly well with those of the latter in the incidence of hypertensive heart disease (40 per cent). There is a discrepancy between the incidence of the anginal syndrome in our series (16 per cent) and that of Pardee (62 per cent) and that of Willius (25 per cent). However, the disagreement may be more apparent than real for the following reasons:

Angina pectoris is a symptom which varies with the "pain threshold" of the individual. This can very well account for the difference in the incidence of the anginal syndrome in groups of cases coming from different levels of society. There is certainly a great difference between the clientele of office practice and the type that is seen in a dispensary, where the incidence of luetic aortitis is high and the perception of pain is low.

Again, the difference in the interpretation of the anginal syndrome may be a factor; for the diagnosis of luetic aortitis very often takes in the symptom of precordial pain. Similarly, many a hypertensive case could be classified under the title of angina. But it is generally agreed that narrowing of the coronary, or of a branch, is the most frequent cause of the angina of effort; the pathologic changes underlying this syndrome are, however, admittedly various.

Therefore, we feel that the agreement between the total number or total percentage of cases having conditions that may give rise to coronary narrowing in each of the series of cases reported is just as important and as instructive as the agreement between the incidence of the anginal syndrome would be. Hence, if we add our

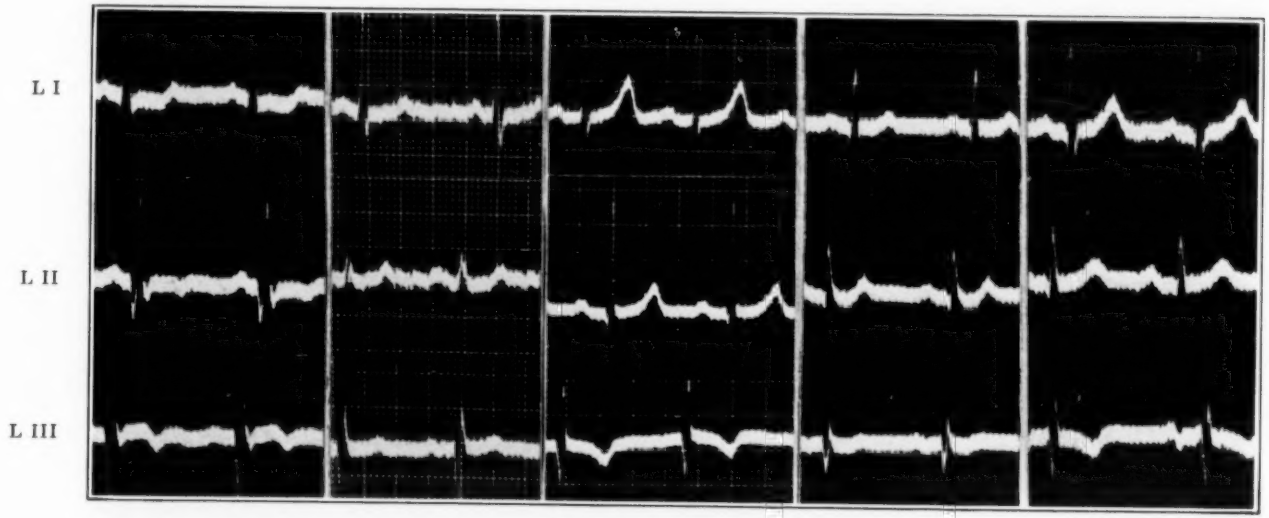

FIG. 1.—Large *Q* waves in Lead III of various types.

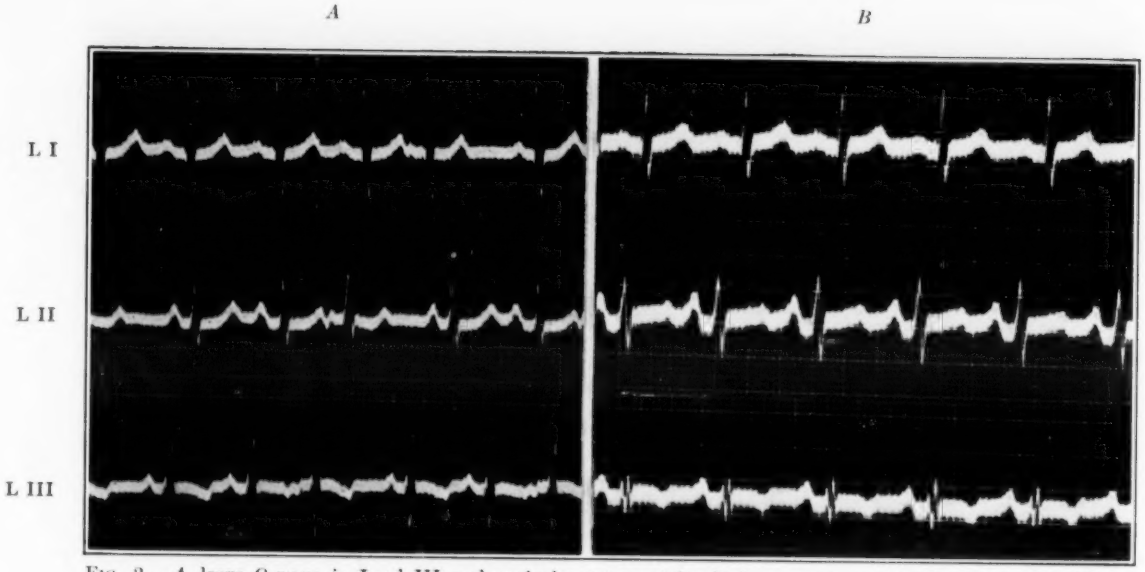

FIG. 2.—*A*, large *Q* wave in Lead III and auricular extrasystoles during pregnancy; *B*, disappearances of both abnormalities 1 year after delivery.

hypertensives, anginal syndrome cases, luetic aortitis and arteriosclerosis we get the sum of 54 cases out of 75 (72 per cent) that exhibit the large Q–3 (Table 1), as compared to Pardee's[4] total of 81 per cent, and Willius'[5] total of 89.8 per cent. Although these figures do not exactly agree, yet they are close enough to signify that this large Q–3 is evidently closely associated with pathologic changes that may involve the coronary arteries, or produce myocardial fibrosis.

The incidence of rheumatic hearts in our series with the large Q–3, 12 cases out of 75 (16 per cent) (Table 1), is entirely at variance with that of the other two series. Willius[5] reports an incidence of 3 per cent and Pardee[4] an incidence of 4 per cent. We wish to repeat that we excluded all cases of right axis deviation from this series. Pardee[4] cites the work of Dr. Daniel Porte, who in a series of 23 cases of rheumatic heart disease with pericarditis found 6 cases (26 per cent) with the large Q–3. Pardee comments that there is something about the rheumatic invasion of the heart that gives rise to this abnormality in the electrocardiogram.

In this group of rheumatic hearts we have only 1 case of aortic stenosis, a patient, aged 59 years, and 1 case of mitral and aortic disease, in a child, aged 11 years. The rest showed involvement of the mitral valve alone. One was 3 years, 1 was 4 years, 2 were 10 years, 2 were 13 years, 1 was 46 years, 1 was 7 years of age, and the age of 2 was not recorded. The youngest children were in the active stage, having fever and tachycardia.

In analyzing the remaining 9 cases of the series with the large Q–3 wave we find varied conditions (Table 1), not unlike the miscellaneous group in the series of cases of Pardee[4] and the cases reported by Willius.[5] It is of interest to note, as in Pardee's series, we have a case of pregnancy with the large Q–3 wave that disappeared following the delivery. The auricular extrasystoles present during pregnancy also disappeared from the tracing following the delivery (Fig. 2). Pardee[4] believes that the high position of the diaphragm favors the appearance of the large Q–3, while a low position is unfavorable.

Another interesting fact is the scarcity of normal hearts in this series of abnormal electrocardiograms. As mentioned previously, our files contained a number of tracings of normal hearts, and the incidence of apparently normal hearts in these 75 cases with large Q–3 wave is only 2 (2.6 per cent). One record is that of a student who has a high diaphragm and whose heart is of the hypersthenic type. In discussing the occasional occurrence of a large Q–3 in electrocardiograms of apparently normal hearts, Pardee[4] suggested the possibility of an unusual distribution of the branches of the auriculoventricular bundle, as well as of a high diaphragm as contributory factors. The normals in Willius' series comprise 1 per cent while there were none in Pardee's series. The latter,[4] in

reviewing the electrocardiograms of normal soldiers of the records of Dr. A. Cohn at the Rockefeller Institute, the electrocardiograms of normal hearts of patients of A. M. Masters of the Cornell Medical School, and the normal electrocardiograms of Lewis' series, found only 2 records with the large Q–3 waves in 277 tracings of normal hearts.

Associated Electrocardiographic Findings in Our Series of 75 Cases. Left axis deviation was present in 43 out of 75 cases having large Q–3 (57.3 per cent). The greatest incidence occurred about equally in the hypertensive group (76 per cent); in the anginal syndrome (75 per cent) and in the arteriosclerotic (75 per cent), while in the group with luetic aortitis there were only 44 per cent. In the rheumatic group (aortic and mitral) only 1 case in 16 (8.3 per cent) was seen with left axis deviation.

The direction of the T wave was normal in the majority of cases in this series (70 per cent). That is, they were upward in all leads or upward in Leads I and II and downward in Lead III. This compares well with Willius'[5] figures of normal T waves (71.4 per cent), while Pardee's[4] figures are somewhat lower (63 per cent). The incidence of significant T wave negativity in the various conditions is interesting as seen from the following figures: The arteriosclerotic showed significant T wave negativity in 50 per cent of their number; the luetic aortitis showed this feature in 44 per cent, the anginal group 41.6 per cent and the hypertensive 32 per cent; the rheumatic group showed none.

The occurrence of T wave negativity according to leads in our series varies greatly from that of Pardee.[4] He states that the frequency of T_2 and T_3 inversion in his series to be 25 per cent as compared with T_1 and T_2 inversion of 11.5 per cent. In our series the ratio is reversed. T wave negativity in Leads II and III occurred only in 5.2 per cent while 21 per cent of our series displayed T wave negativity either in Lead I or in Leads I and II (Table 2). Our figures compare well with Willus' group, 19.6 per cent of cases displaying negative T_1 or T_1 and T_2, and only 9 per cent displaying negative T_2 and T_3. This ratio is in accord with the conception that there was strain predominantly on the left ventricle and conforms to the view of Barnes and Whitten[7] regarding T wave negativity.

Pardee comes to the same conclusion, although T_2 and T_3 negativity predominates in his group. The latter finding together with the clockwise rotation of the vectors of the Q–R–S group in these tracings he considers as features depending on right ventricular activity. Hence, he concludes that the large Q–3 indicates disease of the left ventricle, so that the right ventricle predominates during the spread of the contraction in spite of the left axis deviation or normal axis direction of the Q–R–S.

In this group of 75 cases the only significant electrocardiographic

finding in 53 cases (70.7 per cent) was the large Q 3. Hence, it seems that the large Q 3 is a significant electrocardiographic feature, and when present without any other abnormality may be looked on as being an additional diagnostic sign. It appears to occur most often in diseases exerting their influence predominantly on the left ventricle, whether the anginal syndrome is present or not. The incidence of the rheumatic group in our series is the greatest so far reported. Either there is an actual damage to the left ventricular muscle as suggested by Pardee, or it may be due to the effect of a considerable septal displacement because of the hypertrophy, especially in advanced rheumatic hearts, as suggested by Fenichel and Kugel.[6]

TABLE 2.—ASSOCIATED SIGNIFICANT T WAVE NEGATIVITY.

	Cases.	Per cent.
Lead I	7	9.3
Leads I and II	9	12.0
Leads II and III	4	5.3
Leads I, II and III	2	2.6
Total	22	29.2

Summary. 1. Seventy-five cases with a large Q–3 wave are presented.

2. The majority of these records (54 cases, or 72 per cent) occurred in patients in whom there is apt to be involvement of the coronaries or their mouths, fibrosis of the myocardium, or cardiac hypertrophy with functional strain on the left ventricle.

3. Clinically these patients had one of the following conditions: Hypertensive heart disease (33 per cent), frank anginal syndrome (16 per cent), luetic aortitis (12 per cent) and arteriosclerosis (10.5 per cent). All these diseases are known to exert their influence chiefly on the left ventricle.

4. The rheumatic heart group made up 16 per cent of the series—the highest incidence so far reported. More investigation is necessary for the corroboration and interpretation of this finding. The remaining 9 patients (12 per cent) had miscellaneous conditions, some of whom had diseases that exert their influence on the left ventricle.

5. Left axis deviation was encountered in 43 cases (57 per cent).

6. T wave negativity was seen only in 29 per cent of the cases, the negativity in T_1 and T_2 predominating (21 per cent).

7. One transient Q–3 wave was observed in a pregnant woman. In the tracing 1 year after delivery it was absent.

8. Of the entire group, only 2 apparently normal hearts displayed this abnormal Q–3 wave (2.7 per cent).

Conclusion. The result of our study of the large Q–3 wave in our series compares favorably with that of the other series of cases reported, both in regard to the type of condition in which this abnormality is found and to the scarcity of this finding in normal hearts.

This abnormality in the electrocardiogram may be considered an additional diagnostic sign. It is rarely found in normal hearts and is usually associated with diseases that exert their influence chiefly on the left ventricle.

NOTE.—We wish to thank Miss Dorothy Sherman, the electrocardiographist at the Research Hospital, for her technical assistance in the preparation of this paper.

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GAUCHER'S DISEASE: REPORT OF 2 CASES, WITH A REMISSION IN 1 FOLLOWING ADMINISTRATION OF LIVER EXTRACT.

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GAUCHER'S disease, first described by that author,[8] in 1882, as "primary idiopathic hypertrophy of the spleen," is a relatively rare constitutional disturbance. We report below 2 cases seen in the University Hospital, 1 successfully treated by splenectomy and 1 with a remission now lasting over a year, following our administration of liver extract. We have been unable to find in the literature any instance of a similar remission either in the symptoms or by diminution in the size of the spleen, the only palliative measure mentioned being splenectomy which is not regarded as influencing the eventual course of the disease.

Incidence. The literature pertaining to Gaucher's disease includes several summaries[6,9] of all authentic cases reported. The other cases[1,4,10,13,19] which do not appear in these tabulations, together with the 2 cases seen by us, brings the total number to over 100 reported instances of the disease.

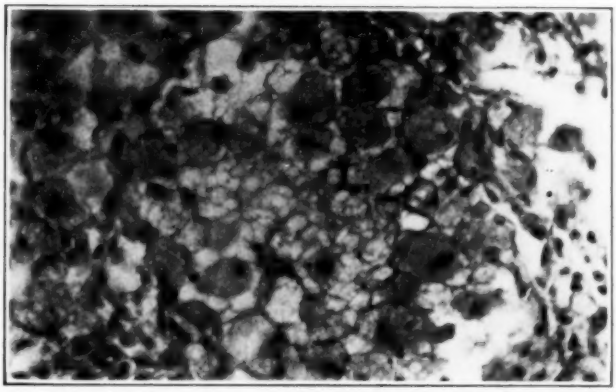

FIG. 1.—Case 1. Section of spleen, showing large Gaucher cells in reticulum of spleen.

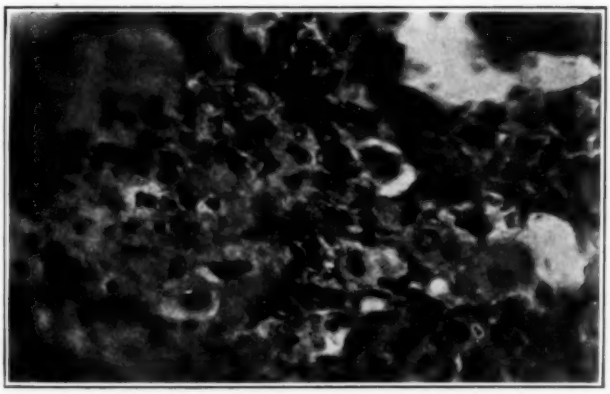

FIG. 2.—Case 2. Section of bone marrow with replacement of normal constituents by large closely packed cells characteristic of Gaucher's disease.

FIG. 3.—Case 2. Roentgen rays of right femur which show the diffuse expansion of the lower end of the femur. Note the mottled oval-shaped areas of decreased density with marked thinning of the cortex and absence of periosteal reaction.

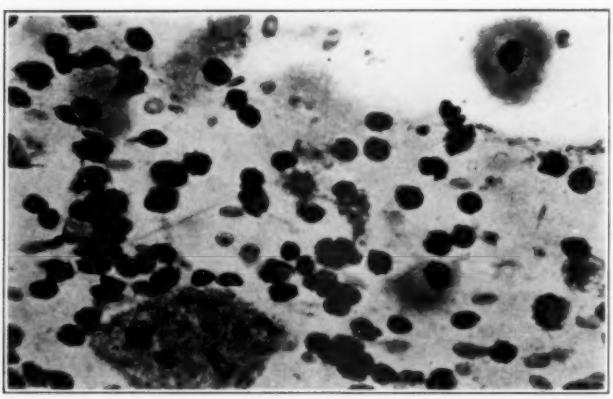

FIG. 4.—Case 2. Material from splenic puncture (dry film Wright's stain). Several Gaucher cells are seen in the preparation illustrating their comparative size and the character of the cytoplasm.

Pathology and Clinical Findings. The most recent complete information regarding Gaucher's disease has been written by Rowland,[18] who has made an exhaustive study of the diseases of lipoid metabolism, and who has seen perhaps more cases of Gaucher's disease than anyone in this country today.*

Gaucher's disease is regarded as a disturbance of the lipoid metabolism with the production and accumulation of a complex lipoid known as kerasin, the biochemical nature of which was established by Epstein.[7] This work has been confirmed by Cushing and Stout,[6] Bloom and Kern[3] and Beumer.[2]

The clinical picture of the disease is often quite clear and the diagnosis readily made. The course of the malady is chronic, with an insidious course in early life and often extending over a long period of years. Death from the disease itself is uncommon, usually being due to anemia and intercurrent infections.

Bone Changes. Gross skeletal changes in Gaucher's disease, pointed out by Pick,[17] in 1922, have excited interest following the radiographic observations of Klercker[14] and Junghagen,[12] in 1926. In some instances the bone lesions have been a predominate manifestation of the disease which has led to the diagnosis, since the radiographic studies are characteristic. The changes usually seen are: (1) Thickening of the shafts of long bones; (2) localized swellings over bones; (3) pathologic fracture. The patient may complain of pain and tenderness over the involved bone, or of difficulty on joint motion. Pain, swelling, redness and exquisite tenderness to palpation may occur over a bone to a degree that the condition simulates osteomyelitis and operation may even be done for that diagnosis. This occurred in 1 of the cases seen by us (Case 2) and has also been reported by Moschcowitz[16] and by Welt.[19]

Case Reports. CASE 1.—L. M. (No. 162212), female, aged 12 years, colored, was admitted to the University Hospital, February 10, 1927, with an abdominal tumor which had been present 2 years with a gradually increasing size. Increasing pallor had been noted for 1 year, and frequent epistaxes for 2 years. The past history was unimportant. There was no history of a similar illness in the family.

Physical examination showed an underdeveloped and undernourished negress. There was nothing unusual about the skin or eyes. The spleen was greatly enlarged, extending 2 inches to the right of, and 2 inches below the umbilicus. The liver extended 3 fingerbreadths below the rib margin. The peripheral lymph glands were not enlarged.

Blood studies: The hemoglobin was 60 per cent (Sahli); red blood cells, 3,320,000; white blood cells, 5900; differential count was normal. The platelets were 150,000. The blood chemistry was entirely normal, including the blood sugar, nonprotein nitrogen, blood chlorid, blood cholesterol, serum protein, albumin and globulin and the erythrocyte fragility test.

Biopsy of the lymph glands and of rib bone marrow were normal. A preoperative diagnosis of Gaucher's disease was made, and on June 13, 1927,

* See also the 1932 Dunham Lectures by Prof. Ludwig Pick, shortly to appear in this Journal. (EDITORS.)

the spleen was removed. *At operation* the spleen was greatly enlarged and had many adhesions, but on gross examination was not unusual.

Histological examination (Dr. C. V. Weller): "The spleen is characterized by an extraordinary hyperplasia and hypertrophy of the reticuloendothelial cells lining the greatly dilated blood sinuses. The lymph follicles are preserved and there is no evidence of a leukemia or other lymphoblastomatous condition. Frozen sections show the large cells lining the sinuses to be free from complex stainable lipoids. The spleen, therefore, falls into the more restricted type of Gaucher's disease in contrast to the type with stainable lipoids which is now called Niemann's disease" (Fig. 1). Stains for iron were not done.

The patient improved rapidly following this operation and was discharged in 6 weeks with the hemoglobin 72 per cent and red cell count 4,800,000.

CASE 2.—A. U. (No. 262321), male, aged 17 years, Austrian (parents), was admitted to the University Hospital, April 7, 1931, complaining of severe pain of 3 days' duration in the lower third of the right thigh. For 11 years he had had recurrent attacks of pain in the long bones of the lower extremities and 7 operations had been done upon the bones of the legs. Healing had occurred in from 3 weeks' to 1 year's time.

Past history: Frequent severe epistaxes had occurred at intervals for several years.

Family history: Seven brothers living and well, with no affection similar to that of the patient, and 2 brothers dead, cause unknown. No familial diseases known.

Physical examination showed a boy of the stated age with a normal physical and mental development. *Skin* was sallow, with a brownish pigmentation over the cheeks and temples. The mucous membranes were pale and colorless. *Eyes* showed wedge-shaped translucent plaques of yellow fat on the nasal sides of the conjunctivæ, the bases of the wedges being toward the irides. *Liver* was felt 3 fingerbreadths below the right costal margin. *Spleen* was felt 2 fingerbreadths below the left costal margin in the anterior axillary line and extended to the right past the left midclavicular line. The edge was smooth and the notch could be felt. *Extremities:* Healed incisions were present on the right thigh and over the right and left legs. The lower third of the right femur was thickened and exquisite tenderness was elicited on pressure. *Lymph glands* of the peripheral group were normal. The temperature was 101° F.; hemoglobin, 50 per cent (Sahli); red blood cells, 3,900,000; white blood cells, 8000. Urine and blood Kahn were negative.

Roentgen ray films (Fig. 3) showed a symmetrical enlargement of the lower half of the right femur with a thin cortex and a large oval area of decreased density just above the condyles. A small irregular area of increased density in the middle of the shaft suggested sequestration, and a diagnosis of chronic osteomyelitis was made.

Clinical course: The right femur was explored through a lateral incision the day of admission. There was edema over the periosteum and through a window in the cortex, the medulla was found filled with a chocolate-colored gelatinous material which gave no bacterial growth on culture. A small sequestrum was removed. Microscopic examination of the tissue removed showed no inflammatory reaction, the bone marrow being replaced by large xanthomatous foam cells resembling those of Gaucher's disease (Fig. 2).

Complete studies were then made on the blood and showed normal blood nonprotein nitrogen, calcium, phosphorus, cholesterol and bilirubin. The bleeding and clotting time, erythrocyte fragility and glucose tolerance tests were normal.

Roentgen ray films of all the long bones were then made and showed involvement of the left femur and both tibiæ by a lesion similar to that seen in the right femur.

The patient was repeatedly transfused, with no improvement. In April, 1931, on the advice of Dr. R. Isaacs, the patient was given liver extract (Lilly), 4 vials daily. Many red blood cells were oval and in measuring them (stained) 12 per cent were smaller than 7.5 micra and 23 per cent larger. The tendency to large oval forms suggested the possibility that liver extract would have a somewhat similar action on the bone marrow to that in pernicious anemia, where oval macrocytes are characteristic.

Except for short periods, he has continued to take 3 to 4 vials daily up to the present time, a period of 11 months. There has been during this period a progressive improvement and at present the patient looks and feels better than he has for many years. The pigmentation over the face has disappeared and the plaques on the eyes are much less noticeable. Epistaxes are very infrequent. There has been a decrease in the size of the spleen and to a lesser degree of the liver. The blood (March 3, 1932) shows the hemoglobin, 66 per cent (Sahli); red blood cells, 4,500,000; white blood cells, 7800. The differential smear and platelets are normal.

Histologic examination (Dr. C. V. Weller) of material obtained by splenic puncture (Fig. 4): "Scattered through the large amount of blood there are huge mononucleate and binucleate endothelial cells with a finely vacuolated cytoplasmic reticulum. Since the contents of these vacuoles do not give positive results with the ordinary fat dyes this corresponds to Gaucher's disease." Stains for iron were not done.

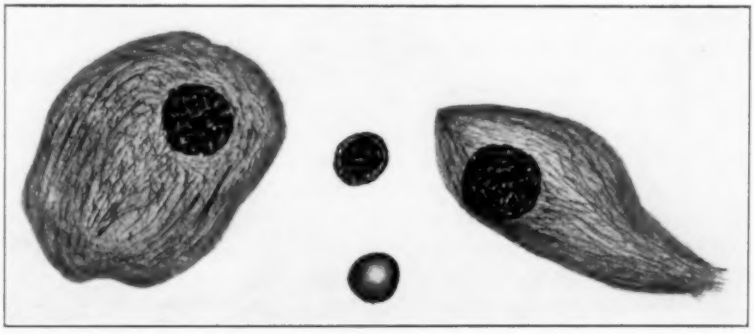

FIG. 5.—Case 2. Cells from splenic puncture material (dry film Wright's stain). The fibrillar character of the cytoplasm is shown. A red blood cell and a small lymphocyte are shown to indicate the relative size. (Drawn by Dr. R. Isaacs.)

Comment. Case 1 who had splenectomy has never returned to the clinic and we have been unable to trace her since making this study.

In Case 2 operation was done before the correct diagnosis had been made, but microscopic examination of the tissue removed at operation and later by splenic puncture proved the diagnosis. The anemia which was present was of major importance, since, as is the rule in Gaucher's disease, transfusions were of no help, the blood picture, in fact, being lower following 2 transfusions than it was previously.

The use of liver extract was suggested on a purely empirical basis. It was felt that since this substance was of proven value in the treatment of primary anemias, as well as in some other

varieties,[11] it might prove helpful in Gaucher's disease for which, to our present knowledge, there is no cure. Splenectomy, which has a favorable influence upon the hemorrhagic diathesis in about 50 per cent of cases, has no effect upon the disease itself, and carries an operative mortality of 25 per cent.

Although we earnestly wish to disclaim the idea of a cure for Gaucher's disease by the use of liver extract, it seems probable that the remission of both subjective and objective findings during the administration of liver extract is more than coincidence. This appears especially tenable since all published reports of the disease characterize it as progressive and not subject to remissions.

Reduction in size of the spleen has not been previously reported in connection with Gaucher's disease, and even though careful measurements, checked by several examiners, had failed to show actual diminution in its size, a Gaucher spleen remaining the same size for a year would be unusual.

In regard to the manner in which liver extract may have acted in this case, we are unprepared to venture any theory, but offer the suggestion that the procedure may be of some value in the future treatment of this disease.

Summary. 1. Two proven cases of Gaucher's disease are added to the reported cases which now total over 100.

2. The first case was improved immediately following splenectomy, but no recent checkup has been possible.

3. The second case had bone lesions mistaken for osteomyelitis and operation was done for this diagnosis.

4 This case was then given liver extract (Lilly) over an 11-month period with the occurrence of a remission characterized by symptomatic improvement, diminution in the size of the spleen and liver and improvement in the blood picture.

5. Although lacking any knowledge of the *modus operandi*, liver extract is suggested in the treatment of Gaucher's disease.

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UNDULANT FEVER.*

SOURCES, MODES OF INFECTION, AND PROPHYLAXIS.

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STUDIES of undulant fever in the United States have been in progress for only the last 5 years, but in this short interval much has been learned concerning the disease in man and the source of the infection. The evidence thus far accumulated indicates that domestic animals, principally cattle and swine, are the chief hosts of Brucella abortus, and transmit the infection to the human family through dairy products and by contact. The methods leading to the control and ultimate eradication of infectious abortion in animals and the prevention of undulant fever are, comparatively speaking, simple, but from a practical standpoint are difficult. The chief difficulties, we believe, are a lack of information on the part of the animal owner, and the great economic factor involved.

The incidence of Brucella abortus infection in cattle in the United States has been found to be from 15 to 20 per cent, while in swine we[1] observed 1.5 to 2 per cent of about 4000 samples of blood to show abortus antibodies. In this country no data are available on animals such as sheep, goats, birds, etc., but basing our judgment on published reports, we consider that the disease in these species is relatively uncommon and that, in general, the danger to man is negligible. An exception to this statement, however, is the Brucella melitensis infection in goats of the southwestern states. We wish to emphasize that any species of animal infected with the genus brucella is a potential danger to man.

Many of those engaged in the animal industry are not aware of the extent of Brucella abortus infection in animals, and do not appreciate that many seemingly normal animals are carriers of the organism and will spread the disease to susceptible animals. If an animal aborts it seldom shows other clinical signs of disease unless secondary infection takes place. The great natural resistance of swine and cattle, and also the frequently acquired immunity to

* This work was made possible by a research grant from the Metropolitan Life Insurance Company. Part of this work was done in the Department of Pathology, Albany Medical College, Albany, N. Y.

the causative agent, have resulted in underestimating the economic losses to the live stock industry and the hazard to the human family.

In 1924, when the attention of bacteriologists in this country was attracted by Keefer's[2] report that Brucella abortus had been isolated from the blood of a patient who had suffered from a continuous fever of several weeks' duration, we had access only to the information on Malta fever, made available by the English Mediterranean Fever Commission. At present we have many data on the incidence and course of the disease in man and animals, modes of infection, dissemination of the virus and some information concerning the pathology of the disease. Although we can be certain that Brucella abortus is the infective agent, we need more data on methods for identifying those strains pathogenic for man. The treatment of the disease is still far from being satisfactory. During the last four years many laboratories have begun studies on some phase of Brucella abortus infection, and nearly all of the larger laboratories engaged in routine work are prepared to make examinations for evidence of disease due to this organism. There are now more than 100 cases of undulant fever diagnosed each month in the United States.

The prevention of any disease demands a knowledge of the source of the virus, how the virus gains entrance to the body, and how an individual may be immunized to that virus if the tissues are invaded. We have considerable information concerning the first two factors in undulant fever, but only a few data on immunity to this infection.

Man may become infected either by consuming dairy products containing Brucella abortus or by wound infection. In this report it seems unnecessary to submit all the data that have been published concerning sources of infection. After the organism has gained entrance to the digestive tract, it invades the normal or diseased mucous membrane, thereby passing into the blood stream directly or indirectly by way of the lymphatic system. The lymphatic and blood stream may become invaded more directly by infection from the tonsils. Experimental work[3] on feeding calves Brucella abortus in milk showed that the lymph nodes draining the mouth and the pharynx became invaded first and harbored the organism longer after the infective milk had been withheld than any other tissues in the body. Several investigators have isolated Brucella abortus from human tonsils after surgical removal. In our own series we observed the organism in 8 of 56 pairs.[23]

Although we know of no instance in which Brucella abortus has been isolated directly from a wound in man, it is evident that undulant fever may result from the infection gaining access to the tissues through a wound. It seems unlikely that the invasiveness of Brucella abortus is great enough to permit it to penetrate the unbroken human skin, although there is evidence to show that this

is possible in guinea pigs. Hardy, Hudson and Jordan[4] reported infection of guinea pigs when cultures of Brucella abortus were placed on the unabraded skin. They observed that, in general, porcine strains were more invasive for the skin of the guinea pig, while bovine strains caused a higher percentage of infections when introduced into the digestive tract.

TABLE 1.—RESULTS OF FEEDING CULTURES OF BRUCELLA ABORTUS TO GUINEA PIGS.*

Bovine.					Porcine.				
Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.	Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.
802	12,000,000,000	+	+	+	781	12,000,000,000	+	+	+
801	3,000,000,000	+	+	+	780	3,000,000,000	+	+	+
800	750,000,000	+	+	+	779	750,000,000	+	+	+
799	187,500,000	−	−	−	778	187,500,000	+	+	+
798	46,875,000	+	+	+	810	46,875,000	+	+	+
797†	11,718,750	+	+	+	811	11,718,750	−	−	−

* The series of multiple dilutions were made by diluting a 12,000,000,000 suspension with equal parts of a sterile physiologic salt solution, discarding every other dilution.

† 9 animals in each series given increasingly weaker suspensions were negative to all 3 tests.

TABLE 2.—RESULTS OF PLACING CULTURES OF BRUCELLA ABORTUS ON UNABRADED SKIN OF GUINEA PIGS.*

Bovine.					Porcine.				
Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.	Guinea pig No.	Suspension.	Lesions.	Culture.	Blood serum.
754	12,000,000,000	+	+	+	796	12,000,000,000	+	+	+
750	3,000,000,000	+	+	+	795	3,000,000,000	+	+	+
753	750,000,000	+	+	+	776	750,000,000	+	+	+
770	187,500,000	+	+	+	777	187,500,000	+	+	+
755	46,875,000	+	+	+	774	46,875,000	+	+	+
751	11,718,750	−	−	−	775	11,718,750	−	+	Slight
752	2,929,687	−	−	−	759	2,929,687	−	−	−
771	732,421	−	−	−	745	732,421	+	+	+
793†	183,105	−	−	−	772	183,105	−	−	−

* The series of multiple dilutions were made by diluting a 12,000,000,000 suspension with equal parts of a sterile physiologic salt solution, discarding every other dilution.

† 7 animals in each series given increasingly weaker suspensions were negative to all 3 tests.

We have recently completed a similar experiment to determine whether guinea pigs are more readily infected with Brucella abortus

by feeding or by skin inoculation. Porcine and bovine strains were used in these studies, and although we observed very little difference between the invasiveness of the two strains for guinea pigs, our data are in accord with those of Hardy and his collaborators. (Tables 1 and 2.)

After it had been determined that guinea pigs can be readily infected by placing bovine and porcine strains of Brucella abortus on the unabraded skin, we desired to find out what effect the application of disinfectants would have on these areas after inoculation. One-tenth cubic centimeter of a suspension containing 12,000,000,000 organisms per cubic centimeter was placed on the skin and spread over the area with a quartz spatula. The area of skin used was about 1 cm. in diameter and located posterior to the base of the ear. This area is very satisfactory because it is devoid of hair, hence requiring no treatment before applying the culture. This area is also difficult for the guinea pig to scratch with his feet and thus contaminate his food and infect the digestive tract. Two guinea pigs were used for each inoculation, which were kept in individual cages. Ten minutes, 30 minutes and 4 hours after the culture had been placed on the skin of each group applications of the following disinfectants were made over the areas inoculated: 5 per cent solution lysol, 1 to 1000 aqueous solution bichlorid of mercury and 70 per cent alcohol. The inoculated area of a fourth group was washed with a 12 per cent solution of ivory soap and water. The guinea pigs were autopsied from 4 to 5 weeks later and examined for evidence of Brucella abortus infection. The results were striking because, in practically every instance (Table 3) infection followed the inoculation, regardless of the application of disinfectants. At present we are continuing this experiment to determine whether other disinfectants are more efficient, and just how rapidly the microörganisms pass through the normal skin of the guinea pig. The results obtained from the studies on guinea pigs are only indicative of what may occur in the human. The integument of man is much thicker than that of the guinea pig, and doubtless the resistance to extraneous infection is thereby proportional.

TABLE 3.—NEGATIVE RESULTS OF APPLYING DISINFECTANTS TO SKIN OF GUINEA PIGS UPON WHICH CULTURES OF BRUCELLA ABORTUS HAD BEEN PLACED.

Disinfectant.	Time. 10 minutes.		30 minutes.		4 hours.	
	B	P	B	P	B	P
Bichlorid of mercury, 1 to 1000	+	+	+	+	+	+
Lysol, 5 per cent	+	+	+	+	+	+
Ivory soap and water	+	+	+	+	+	+
Alcohol, 70 per cent	+	+	+	+	+	+

B, bovine; P, porcine.
2 guinea pigs used for each disinfectant and each interval.—Total of 48.

It is evident that man may become infected with Brucella abortus from an invasion of the normal conjunctiva with or without the

development of lesions of the eye. An infective exudate could spatter into the eye, or be introduced by a finger contaminated with the organism. A laboratory worker, especially, is exposed to such hazards. Schroeder and Cotton[5] demonstrated experimentally that they could infect guinea pigs with the bovine and porcine strains of Brucella abortus by introducing into the eye 1 drop of a saline suspension of the organism. Only one-third of the animals receiving the bovine strain showed lesions of abortion disease at autopsy, while all of those inoculated with the porcine strain became infected. In only 1 case was the eye observed to be diseased grossly. Later they[6] inoculated a heifer by placing 1 drop of a Brucella abortus suspension in one eye. The animal became infected and aborted in 54 days.

Orloff[7] has recently reported 2 patients with undulant fever, who showed extensive lesions of the eye during the course of the disease. He also described lesions observed in the eyes of 19 guinea pigs experimentally infected with Brucella abortus. He observed a parenchymatous keratitis, iritis, iridocyclitis, choroiditis, neuroretinitis and an inflammatory cataract. He states that the lesions produced by Brucella abortus are very similar to those resulting from tubercle bacillus infection of the eye, and no doubt many cases of the former are erroneously diagnosed. Such information emphasizes the fact that when handling tissues or suspensions containing Brucella abortus precaution must be taken to avoid eye infection.

We believe that there are three groups of individuals who are exposed to infection with Brucella abortus and Brucella melitensis: (1) Consumers of dairy products; (2) animal husbandrymen and the handlers of fresh meats; (3) veterinarians and laboratory workers engaged in research on infectious abortion, or in the routine examination of material for evidence of abortus infection. This grouping is purely arbitrary because those composing the second and third groups may likewise be classed with Group 1 when they are exposed to the infection from drinking raw milk. But in as much as the methods of prevention of the infection in each instance are so different this classification serves our purpose well.

We could simplify this report by stating that the eradication of infectious abortion in domestic animals would prevent undulant fever in man. This is the ultimate goal of those engaged in the control of abortion disease. However, from our knowledge of infectious disease, we realize that unless a cure for this malady is discovered, the elimination of the disease by the Bang method will require a half century or perhaps longer, and many cases of undulant fever will occur in the meantime.

Brucella abortus is not extremely pathogenic for man, or we may say that the human family is not very susceptible to infection with this organism. But we do not know whether this organism is just beginning to adapt itself to man, or whether undulant fever

has not been recognized in the United States until recently. In our opinion, both factors have been operating, but because of this recent knowledge that there is danger to man, greater control measures will be taken to prevent further spread of the disease in animals.

The examination of a comparatively large number of human blood samples from various states shows that from 5 to 7 per cent of those individuals living in the country or in small towns, or cities where most of the milk sold is not pasteurized, carry abortus antibodies in their blood. This indicates that many no doubt have developed an active immunity to the infection. This may be the result of a mild infection unrecognized, a case of undulant fever diagnosed as due to some other infection or due, perhaps, to the ingestion of living organisms without causing symptoms of disease.

The first group, the consumers of dairy products, are exposed chiefly by drinking raw milk or cream containing the infective agent. Pasteurization of milk from cows infected with Brucella abortus will protect this group. Arnold[8] reports that it requires a temperature of 140° F. for 40 minutes to destroy the porcine type of Brucella abortus, and that the temperature and length of time at which milk is ordinarily pasteurized, *i. e.*, 140° to 145° F. for 30 minutes, will not kill the most pathogenic strains of Brucella abortus. Yet the abundance of evidence indicates that pasteurization does destroy Brucella abortus.

In 1928 we[9] reported our findings concerning the effect of temperatures of 140°, 142° and 145° F. on cultures. A total of 8 cultures were studied, 4 bovine, isolated from milk, 3 human and 1 porcine. The porcine culture was more resistant than most of the human and bovine strains. It required 20 minutes at 140° F., 15 minutes at 142° F. and 10 minutes at 145° F. to render it nonviable. One bovine and 1 human strain were as resistant to the process as the porcine type. The remaining strains examined were not viable after 15 minutes at 140° F., 10 minutes at 142° F. and 5 minutes at 145° F. Recently we[10] determined the thermal death time of 10 extremely virulent so-called porcine strains of Brucella abortus isolated from swine and man. Heating the cultures in milk for 30 minutes at 142° F. killed all of the organisms, demonstrating again that our present requirements for the holding method of pasteurizing milk are adequate to kill Brucella abortus. MacFadyean and Stockman,[11] of England, Zwick and Wedeman,[12] of Germany, and Park[13] have likewise reported that Brucella abortus is destroyed by these temperatures.

We have studied this problem from three different standpoints: (1) The thermal death time of human, bovine and porcine cultures of Brucella abortus; (2) the examination of 205 samples of pasteurized milk and cream from 50 cities and towns in 5 states for evidence of the infection; (3) the incidence of undulant fever in communities

before and after ordinances were passed requiring raw milk to be pasteurized or to be free from Brucella abortus.

TABLE 4.—EXAMINATION OF PASTEURIZED SAMPLES OF MILK AND CREAM FOR BRUCELLA ABORTUS.

State.	Number of cities and towns.	Number of samples of milk and cream.	Results of guinea pig injection.
New York	39	152	Negative.
Massachusetts	7	18	Negative.
New Jersey	2	2	Negative.
Illinois	1	20	Negative.
Indiana	1	13	Negative.
Total	50	205	

Table 4 shows the results of examining 205 samples of pasteurized milk and cream collected from 50 small towns and cities in 5 states. The majority came from New York State, but through the courtesy of Dr. Arnold Kegel, of the Department of Health, Chicago, 20 samples were obtained from Chicago for examination, while Dr. A. S. Giordano shipped us 13 samples from South Bend, Ind. Eighteen samples were collected from the western half of Massachusetts and 2 from New Jersey. The samples were collected from pasteurizing plants, distributing stations, stores and restaurants, packed in ice and taken to the laboratory as soon as possible. The cream was allowed to rise on each sample of milk, after which 2 cc. of the cream were injected subcutaneously into guinea pigs. The same amount of pasteurized bottled cream samples was also injected into the guinea pigs. The guinea pigs were examined for evidence of Brucella abortus infection, approximately 4 weeks after injection. The tissues were inspected for lesions, and cultures were made from the spleen and incubated at 37.5° C. in an atmosphere containing 10 per cent carbon dioxid. Brucella abortus was not recovered from any of the 205 samples examined. Agglutination tests made on the guinea pig serums were likewise negative. When one considers the many different types of pasteurization equipment used, and the varying conditions under which these samples were pasteurized, we feel that this is another general indication of the efficiency and value of the process. Carpenter and King[14] have reported that 20.4 per cent of the raw milk supply of three counties in central New York showed Brucella abortus infection. Evans,[15] Fleischner and Meyer,[16] as well as others, have reported similar findings. Therefore, it is probable that approximately 40 of the 205 samples tested contained Brucella abortus before pasteurization. The temperatures at which these samples were pasteurized varied from 142° to 145° F. for 30 minutes. We have no information on the pathogenicity of the strains of Brucella abortus in the milk nor on the number of organisms present prior to the pasteurization. There have been isolated from milk

samples very virulent strains of Brucella abortus that have been classified by some investigators as porcine types. Therefore, we cannot assume that all were of low virulence and that none would have infected man.

The epidemiology of undulant fever is interesting in that very few cases have occurred in communities where the milk is pasteurized. On the other hand, instances have been recorded of the occurrence of a series of cases on a raw milk route, or in a community where the milk is not pasteurized. As a rule, not more than 1 case of the infection occurs in a family, even though all the members of the family may be drinking the same milk. In those communities where undulant fever has been reported and later ordinances have been passed by the local boards of health requiring either pasteurization of the milk or the elimination of those animals discharging Brucella abortus in their milk rarely have more cases of the disease been diagnosed. A typical example of this may be cited from data obtained from the Board of Health at Ithaca, N. Y., where this work was begun. In 2½ years 17 cases of undulant fever were diagnosed. During this period efforts were made to locate and eliminate the source of the infection. As soon as pasteurization was encouraged, many of the smaller distributors sold their milk to larger dairies, who pasteurized the milk. At present all the milk is pasteurized except that from one dairy that produces a raw milk for babies, and the owner of this herd has eliminated the infected animals. With the exception of a university student who spent the summer months out of the city, no cases of undulant fever have been reported during the past 2 years. Similar evidence has been submitted by Farbar and Mathews[17] on an epidemic of undulant fever with a study of the milk supplied to this community. Studies of patients at the Metropolitan Life Insurance Company Sanitarium[18] before and after Brucella abortus was eliminated from their milk supply demonstrate the value of pasteurization.

Although one occasionally obtains a history from a patient with undulant fever, stating that only pasteurized milk has been drunk, we find in most instances, after careful questioning, that unpasteurized cream has been used on cereals or other uncooked foods. The history of a patient who states that he is not a so-called "milk drinker" often reveals this same information. Patients also forget until questioned that they were on vacations, the guests of friends, or attended social gatherings where the quality of the milk or cream was unknown.

Because many cases of undulant fever occur in the country districts and on farms, where raw milk is consumed and there are no facilities for pasteurizing milk except by boiling, an entirely different problem is presented. The dairy husbandrymen not only suffer the great economic loss from infectious abortion but are also exposed to hazard of contact infection. Pasteurization of milk

does not protect those men engaged in abattoirs, men who slaughter animals, cut, handle and inspect raw meats. Many of these individuals do develop undoubtedly an active immunity, while others, for reasons still undetermined, are susceptible and are incapacitated for long intervals with undulant fever.

To protect this group from the disease, we must either eliminate the infection from our livestock which is the source of the disease for man, prevent infection from occurring through wounds, or immunize man to the infection. At present we do not have satisfactory information to determine whether the latter procedure can be successfully accomplished. The education of the dairyman and those engaged in abattoirs to the dangers of handling infected animals or tissues where wounds are present on the hands or arms is important. Immediate disinfection of wounds, inflicted while working with possibly infected material, is necessary. The use of rubber gloves, or some other protection, when abrasions or open wounds are present, would prevent many cases of undulant fever, especially among abattoir workers. Nevertheless, the eradication of infectious abortion from the livestock industry is urgent. Control methods are well understood by veterinarians and by many laymen. Fourteen states and the territory of Hawaii have already passed laws prohibiting the admission of cattle infected with Brucella abortus. The Federal government, as well as the majority of the state bureaus of animal industry, is actively engaged in research to prevent the further spread of infectious abortion, or is employing control measures.

The method of control is relatively simple. Specific treatment has failed, but the detection of infected animals, followed by their elimination or isolation has proven to be a most satisfactory plan for establishing herds free from the disease. The agglutination test, or "blood test" as it is commonly called, is not 100 per cent efficient and has certain limitations, but it will nearly always determine the infected animals in a herd. Occasionally an animal infected with Brucella abortus will not show antibodies in its blood serum. There are instances where the serum from an infected cow will not agglutinate the abortus antigen for a few days prior to, or following an abortion or parturition. However, it is as efficient as the Widal test for typhoid in man, and is the most important aid in the control of infectious abortion in domestic animals. The blood test requires a well-trained serologist and the interpretation of the results of the test should be made by one who understands the clinical phases of the disease and at the same time has a knowledge of the blood test and its limitations.

The infected animals should be eliminated from the herd or segregated. Because of the economic factor, many dairymen cannot always sell or slaughter the infected cows that may be producing well. In that case, isolation of the infected cattle from the normal

animals may be carried out. If two stables are not available, a temporary partition may be installed to separate the two groups, and with intelligent care a herd free from the disease can be established. Every effort should be made to test the blood of range cattle and to keep the positive reactors from the negative group. The experience gained in the eradication of bovine tuberculosis in animals has proven of great value to those agencies interested in the eradication of infectious abortion. This problem is much simpler than that of bovine tuberculosis because cattle may be tested as often as desired. Furthermore, calves may nurse infected dams with impunity. A higher percentage of cows, though small, recover from the disease than from tuberculosis.

Even though an animal owner is not in a position to dispose of his infected animals or to isolate them, we believe that the blood test is still valuable. The results are an asset to him by showing the status of his herd. With the knowledge that a cow is infected, he may watch her for premonitory symptoms of abortion and isolate her from the herd. This protects uninfected animals from the greatest danger, because the placenta and uterine exudate are the most infectious material and massive doses of the organism are present to spread the disease. The milk from such an animal should not be used for home consumption unless pasteurized. We have studied 2 cases of undulant fever in each of which the milk from the only infected cow in the herd was saved for family use. The animal owner can protect himself or those in his employ by not removing the placenta if it be retained, as usually occurs following late abortions. He should refrain from this, especially if there are wounds on his hands and he does not have the proper disinfectants with which to care for himself. The veterinarian should have this information in order to advise his client if the latter is not aware of such danger. The veterinarian is thus in a position to protect himself and to render a greater service to the livestock industry, for he can extend this information to the farmers and aid in the prevention of undulant fever.

We have stressed the disease in cattle as a source of infection for man, but it must be remembered that Brucella abortus is pathogenic for nearly all species of domestic animals. Goats, sheep, swine, horses and domesticated birds have been found occasionally to be infected with Brucella abortus. The premature expulsion of a fetus from any species is clinical evidence of infectious abortion that should be checked by laboratory tests. Aside from cattle, swine and horses present the greatest danger to man. Many of the porcine strains are extremely pathogenic for the human family, and because of close contact with cattle, swine may transmit very virulent strains to cattle. Brucella abortus has been isolated from such lesions of horses as poll-evil and fistula of the withers. Such localized infections in horses should be handled with great care. The blood test and bacteriologic examinations should likewise be

carried out, and are as valuable in detecting and controlling the disease in these species as they are in cattle. The elimination of Brucella abortus infection in animals protects the butcher, the meat packer and the meat inspector. The value of the blood test cannot be overestimated.

The third group, in which we have included veterinarians and laboratory workers engaged in research on infectious abortion or in the routine examination of material for Brucella abortus, is continually exposed to the infection. Many cases of undulant fever have occurred in such individuals, and although the disease is seldom fatal, it runs a protracted course that has incapacitated the patients for 1 or 2 years, and in certain instances for even a greater period. In the chronicity of the disease lies the seriousness of this infection, and since we have no satisfactory treatment to shorten the course of undulant fever, prophylaxis, such as the disinfection and protection of wounds from invasion by the organism, should be stressed. We see great differences in the susceptivity of individuals who come in direct contact with massive doses of the infection. Certain veterinarians and laboratory workers take no precautions whatever, when they are aware of exposure to the infection, while others, taking the strictest care, develop symptoms of the disease. Individuals possessing a natural immunity may be employed in a laboratory to work with Brucella abortus with impunity. In our laboratory we make it a practice to examine the blood of any new helper when he begins his work, and to test his blood every six or eight weeks. We also make a skin test on the individual when he first enters the laboratory. This consists of injecting intracutaneously 0.1 cc. of a suspension containing approximately 5,000,000,000 killed organisms per cc. This gives us valuable information. I believe it is wise to go one step further, as is done in certain European laboratories, where it is a practice to immunize the laboratory workers by injecting, subcutaneously or intracutaneously, small amounts of killed suspensions of Brucella abortus and Brucella melitensis. It might be well to consider this method of immunization for veterinarians. Killed suspensions of Brucella abortus injected into cattle do produce some temporary immunity, but similar experiments on guinea pigs, followed by the injections of living cultures or other infectious material, have failed. Nevertheless, there is some evidence that such injections in man are valuable and perhaps as efficacious as the injections of killed suspensions of Bacillus typhosus. The protection may last a long time, or it may be permanent. At present we do not have enough available information to be certain of the value of such a procedure, but indications are favorable. Some interesting information has been accumulated on the immunity acquired by veterinarians. Thomsen,[19] of Denmark, tested the blood from several groups of veterinarians: Those who had practised for more than 1 year; a group that had practised 5 months; a group that had practised 1 month; a group of senior

veterinary students who had never practised. The results he obtained were, respectively, 94, 85, 42 and 0 per cent. Some of these men with positive serums had typical cases of undulant fever, some described symptoms suggestive of the disease, while some denied having had any illness whatsoever. He found also that the serum of 10 out of 16 bacteriologists showed abortus antibodies, and, therefore, suggests the vaccination of young veterinarians, caretakers of animals, animal owners and research workers who come in contact with the disease.[5]

Huddleson and Johnson[20] have reported results obtained from testing for abortus agglutinins the serum of 49 veterinarians in Michigan. They found that 57 per cent of the group was positive to the test, and that 26 per cent had a titer of 1 to 100 or higher. Three of the men gave definite evidence of having undulant fever while others either gave vague histories of the disease or denied any such experience. It is evident that this group should be protected and we believe vaccination will afford such protection. Recently Dubois and Sollier[21] reported results on the prophylactic vaccination of man with heat-killed suspensions of mixed strains of brucella, containing 2,000,000,000 organisms per cc. One hundred and eleven persons exposed by contact and by consuming infective dairy products in from 3 to 8 months after vaccination failed to develop undulant fever, while 2 of 36 similarly exposed individuals not vaccinated contracted the disease.

Although undulant fever is rarely transmitted from patients to those caring for them, there is such a possibility. Brucella abortus is isolated from the urine in approximately 10 per cent of the cases. Amoss and Poston[22] have recently reported recovering the causative agent from the stools of patients, suggesting alimentary tract infection. This necessitates the careful disposition of these excretions and bacteriologists working with such specimens should consider them a source of danger.

Summary. 1. Sources and modes of infection are described.

2. Data are submitted, indicating that guinea pigs can be infected by feeding them porcine or human strains of Brucella abortus, or by placing the cultures on the unabraded skin.

3. The application of 5 per cent lysol, 1 to 1000 solution of bichlorid of mercury, 70 per cent alcohol, or ivory soap and water solution to the skin areas of guinea pigs, 10 minutes, 30 minutes and 4 hours after cultures of Brucella abortus had been placed on the unabraded skin, failed to prevent abortion disease.

4. The thermal death time of Brucella abortus is discussed and studies on the pasteurization of milk containing this organism are reported. An examination of 205 pasteurized samples of milk and cream showed no infection with Brucella abortus. Pasteurization will protect the consumer of dairy products.

5. A method for the control of infectious abortion in domestic animals is described. The value of blood testing and isolating or

eliminating infected animals is emphasized. The importance of eradicating the disease in small communities and on farms where facilities for pasteurization are not available is stressed. Boiling of the milk under such circumstances is satisfactory, but a practice difficult to institute.

6. The vaccination of veterinarians and bacteriologists continuously exposed to Brucella abortus is suggested.

7. The proper disposal and care in the examination of urine and feces from patients with undulant fever is emphasized.

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A NEW TYPE OF DUODENAL TUBE TIP.*

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NEW YORK.

(From the New York Post-Graduate Medical School of Columbia University and the New York Post-Graduate Hospital.)

It is the purpose of this article to describe a new type of duodenal tube tip, designed to prevent certain difficulties which occur in nonsurgical biliary tract drainage. In our experince, as well as

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in that of many others, these difficulties have recurred in some cases with any of the duodenal tubes now in use, even under the most expert technique. Our experience is based upon over 2000 drainages, begun 5 years ago under the direction of Dr. Ludwig Kast and continued in the combined Surgical and Medical Gall Bladder Clinic of the New York Post-Graduate Hospital.

A study of the technique of duodenal drainage has indicated that the most common cause of failure has been inability to introduce the tube into the duodenum, the passage of the bucket through the pylorus having been difficult or impossible. Another frequent difficulty has been the regurgitation of the bucket from the duodenum into the stomach, usually following the injection of stimulants such as magnesium sulphate, an occurrence by no means uncommon in those patients having an irritable stomach or duodenum. Difficulty in swallowing the tube has proved a negligible factor.

Credit for the pioneer work in duodenal intubation must be given to Einhorn, Hemmeter and Gross. Further valuable improvements both in instruments and in technique have been contributed by Jutte, Rehfuss, Lyon, Buckstein, Levin, Kohn and Wilkins. Our routine practice has been the use of a metal bucket such as that of Lyons or Rehfuss, which has seemed to us most reliable for the average patient. In difficult cases, however, the Levin catheter-tip tube has sometimes proved more satisfactory.

We have also paid special attention to the maneuver of Dr. Morgenstern in passing the Levin tube under the fluoroscope, by manual manipulation. While the results of this procedure have been spectacular at times, in many cases it has not been successful. The principal difficulty has been the tendency of the tube to loop in the cardiac end of the stomach, above the costal margin, where manipulation is impossible. Moreover the ultimate aim of the technique of duodenal drainage should be a successful drainage without the need of Roentgen ray control, except in cases of suspected organic obstruction of the pylorus.

In view of these difficulties, the author has designed a different type of drainage tube tip, which facilitates passage of the bucket into the duodenum and is more likely to keep it there, even in those patients who are apt to reject the bucket from the duodenum following the use of stimulating fluids. During the past year the new tube has been used successfully in almost all of a series of about 100 cases, most of which had been selected because drainage with other types of tubes proved unsuccessful, in many cases after repeated attempts.

The original tube as designed in 1929 consists of the standard type of tubing which has in place of the usual bucket, a terminal unit of two parts. The proximal of these is a narrow-slotted bucket, attached to a metal ball, $\frac{3}{8}$ inches in diameter, by a thin chain,

1½ inches long. The chain is fastened to the bucket by means of a ball-and-socket joint, the chain and its connections being covered with a waterproof protection which is a section of light, flexible, rubber tubing, tightly tied with silk thread at both ends.

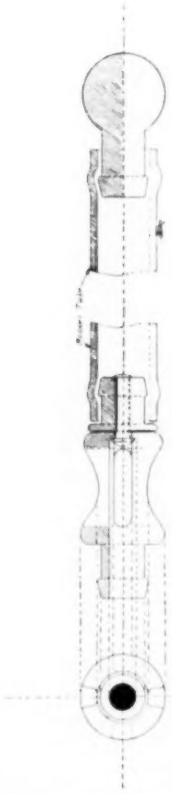

FIG. 1.—Model with shoulders containing grooves for the purpose of preventing obstruction of the slots by collapse of the visceral walls and adherence to the walls by suction.

The bucket is constructed of metal tubing, ¼ inch in diameter, the distal end being turned to enclose the small ball in which the gold-plated chain is imbedded. The other end of the chain is similarly attached to a small piece of metal, square on one end, threaded on the other. The threaded end screws into the brass ball, this arrangement allowing the rubber tubing to be slipped over the chain. The entire unit is gold-plated.

We are now using a similar model with a shorter bucket and swivel joint in the place of the ball-and-socket joint. The ball

has been reduced in size to $\frac{5}{16}$ inch. A further very satisfactory modification of this design eliminates the chain and the swivel joint, the terminal ball being attached to the distal end of the bucket by only the rubber tubing. Shoulders on each end of the bucket, of slightly larger diameter than the tubing, contain longitudinal grooves. This arrangement provides for a free flow of fluid from above or below the bucket, as well as preventing adherence to the mucosal wall by suction, regardless of how constricting the surrounding viscera may be. A special method of tying the thread on the ends of the tubing eliminates knots with their irritation of the esophagus and tendency to untie.

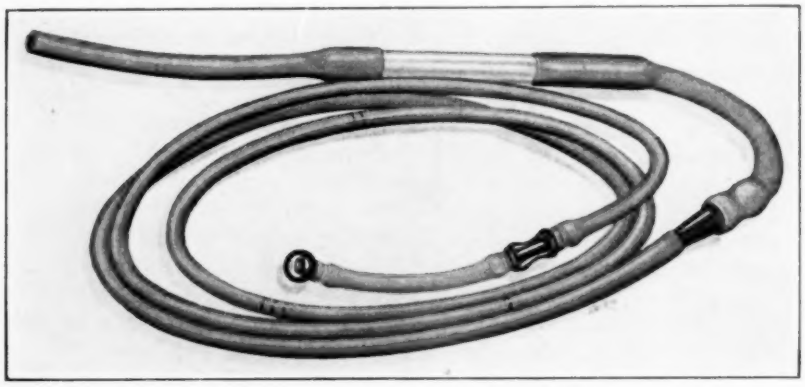

FIG. 2.—Complete tube with glass window.

Materials of which the tip has been constructed include gold and brass, gold-plated. The highly soluble character in hydrochloric acid of brass and most other metals, together with the resultant toxic salts, make the use of an inert metal such as gold essential. Gold-plating is at times not entirely satisfactory, minute defects occur which form an electrochemical couple. The result is rapid corrosion and discoloration of the bucket, the use of buckets having this appearance should never be allowed. A further advantage of gold is found in its specific gravity, which is approximately double that of brass or lead. With a terminal ball of gold, a given weight may be obtained by the use of a ball of half the size otherwise required, which facilitates swallowing and extraction of the tip.

The malleable character of gold renders its use practical from the mechanical standpoint. The cost of a low grade of gold is not greatly in excess of that of inferior metals, the increased expense is offset by its advantages in providing a safe and easily cleaned instrument, which always looks well, and will last indefinitely. Another consideration is the cost of replating and replacing buckets of other types of metal.

The construction of this tube allows greater flexibility and adaptability to irregular surfaces, and to a constricted or spasmodic pyloric ring. The terminal ball acts as a weight, the ball-and-socket or swivel joint eliminates the factor of twisting. The ball being freely carried by the peristaltic action of the stomach to the pyloric orifice enters easily because of its minimum diameter at any angle of entrance. These models can frequently be introduced into the duodenum within 10 minutes with the patient sitting up; when lying on the right side the time of entrance into the duodenum is usually about 20 minutes. In cases of pyloric obstruction a smaller ball may be substituted for the usual size.

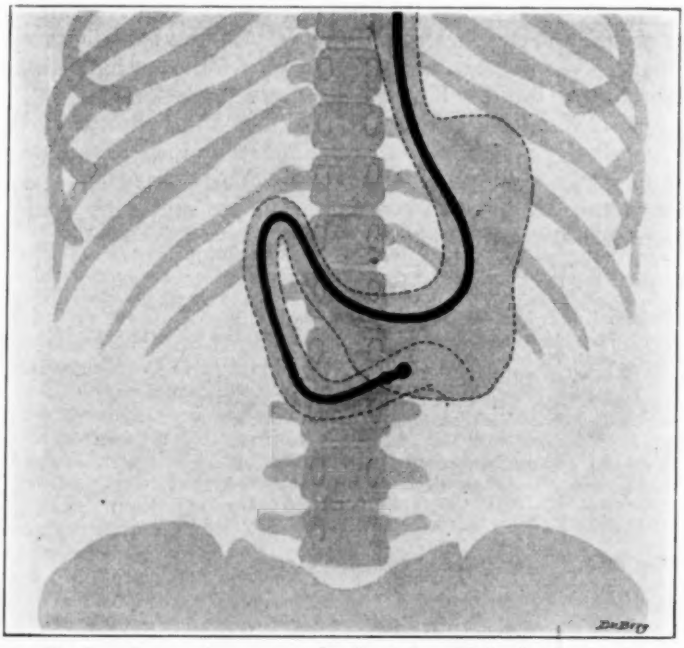

FIG. 3.—Tracing of a roentgenogram, showing tube with bucket in the descending duodenum. Position verified by the ingestion of contrast medium.

Fluoroscopic study has shown the ball to enter the duodenum promptly, drawing the bucket after it. The tube is allowed to descend in the customary manner until the 3-ring mark is at the lips of the patient, after which bile is obtained. The weight of the terminal ball retains the position of the bucket after stimulation, even in cases with an irritable duodenum. We have been more successful with the manual introduction of this tube under the fluoroscope than with any other type. Roentgenogram studies of the tube in position, verified by the ingestion of contrast medium,

have been made through the courtesy of Dr. W. H. Meyer, Director of the Department of Roentgenology.

Concentration of the weight of the tip at the end of a flexible section has proved an advantage. Slots in the bucket of approximately the same width as the inner diameter of the tube prevent as far as possible the obstruction by mucus or débris. Rubber tubing of slightly larger caliber than that now in use provides satisfactory resiliency and tends to prevent looping. A section of glass tubing 3 inches long in the syringe end of the tube insures a sterile tip for taking cultures when the terminal section of rubber tubing is temporarily removed.

Summary. Investigation of the technique in over 2000 biliary tract drainages has shown that in most cases in which results were unsatisfactory or the drainage unsuccessful, the cause was either inability to pass the tube through the pylorus or failure of the duodenum to retain the bucket following stimulation.

A type of duodenal tube tip is described which during the past year has greatly facilitated our technique of drainage, even in those cases in which drainage had been previously reported as being unsatisfactory or impossible. Arrangements are being made for the manufacture of this type.

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REVIEWS.

CYTOLOGY AND CELLULAR PATHOLOGY OF THE NERVOUS SYSTEM. Three volumes. By VARIOUS CONTRIBUTORS. Edited by WILDER PENFIELD, Professor of Neurology, and Neurosurgery, McGill University, Montreal. *Vol. I. Neurones, Nerve Sheaths and Nerve Endings. Vol. II. Neuroglia, Microglia, Bloodvessels, Meninges, Pineal, Pituitary, Eye. Vol. III. Neoplasms, Malformations, Reactions.* Pp. 1280; 886 illustrations, 15 in color. New York: Paul B. Hoeber, Inc., 1932. Price, $30.00.

THESE three volumes, the work of 26 distinguished students of the central nervous system, are a timely and most welcome contribution to the literature of a subject, of interest alike to the general biologist, the neuroanatomist, the neuropathologist, the neurophysiologist and the clinical neurologist. Within the past few years many new methods have been devised which have made possible a more detailed study of the intimate structure of the nervous organs. The harvest reaped has been very great, so great indeed that today's conception of the structure and function of the nervous system in health and in disease is vastly different from that which prevailed a decade or two since. There are few students of this system who have been able to keep step with the rapid march of progress. In these volumes an excellent account is given to what is known at this time of the microscopic structure of nervous tissue. No one man, alone, could have written this account, and wisely, the editor, himself a well-known investigator, has invited collaborators from various countries. The contributions represent the splendid achievements which have come to us from the great research institutes and the universities of the United States, Canada, Sweden, Germany, Holland, Spain, Great Britain and France. The composition of the work demonstrates the care the editor has exercised in outlining the scope and structure of these volumes. Each chapter is from the pen of a writer who, through his own investigations, is most familiar with the treatment of each subject discussed. Volumes I and II take up the intimate structure of the nerves in health and disease from a general viewpoint. In them the anatomy and physiology of each cell group, or each component part of the nervous system, is described and discussed in turn, thus presenting the foundation necessary to the understanding of the several disease entities. The third volume contains studies of certain pathologic entities, and is noteworthy particularly for its splendid discussion of the neoplastic diseases of the nervous system. In order to avoid repetition descriptions of disease entities which are scattered through the first two volumes are not again discussed in the third volume, but are made readily available through an excellent index.

In Volume I Cowdry (St. Louis) discusses the general character of the neurone, Kappers (Amsterdam) the principles of development of the nervous system and Bielschowsky (Berlin) treats the pathologic changes which nerve cells in general may undergo. This chapter serves as a splendid introduction to the histopathology of nerve cells, and should be mastered by all who wish to become familiar with this difficult subject. De Castro (Madrid) contributes two chapters, one on the sympathetic ganglia, the other on the sensory ganglia of the cranial and spinal nerves; both normal and pathologic conditions are considered. Boeke (Utrecht) describes the sensory and motor nerve endings and Nageotte (Paris) the sheath of the peripheral nerves, the structure of nerves and their degenera-

tion and regeneration. In the last chapter Stöhr (Bonn) gives an account of the nerves of bloodvessels, meninges and other structures.

In Volume II Penfield (Montreal) describes normal and pathologic neuroglia, and Del Rio-Hortega (Madrid), the microglia. The choroid plexus and ependyma are dealt with by Agduhr (Upsala), the cerebrospinal bloodvessels by Cobb (Boston), the meninges by Weed (Baltimore), the pineal gland by Del Rio-Hortega, the hypophysis by Bucy (Chicago), the retina, choroid and sclera by Arey (Chicago), and, finally, the optic nerve and papilla by Cone and McMillan (Montreal).

A large part of Volume III is devoted to the tumors of the nervous system. There are chapters on the primary tumor of the brain by Bailey (Chicago), of the sheaths of the nervous system by Penfield (Montreal), of the spinal cord by Kernohan (Rochester, Minn.), the optic nerve by Verhoeff (Boston), the retina by Grinker (Chicago), the chorioid by Friedenwald (Baltimore), the sympathetic nervous system by Bielschowsky (Berlin) and the hypophysis by Bailey. Masson (Montreal) discusses the interesting neural proliferations in the vermiform appendix, and Globus (New York) the malformations of the nervous system. Hydrocephalus and the atrophy of cerebral compression is presented by Penfield and Elvidge (Montreal). The inflammatory cells in the nervous system, a difficult and somewhat controversial subject, is ably presented by Greenfield (London). Finally there is a chapter by Boyd (Winnipeg) on the cells found in the cerebrospinal fluid under normal and abnormal conditions.

There are nearly 900 illustrations, and nearly all of them of exceptional clarity. The index is very satisfactory.

The volumes are fittingly dedicated to the spirit of scientific investigation exemplified in the histologic work of Ramón Y Cajal.

The reviewer would compliment the editor for having well accomplished a difficult task. This work, a truly international undertaking, will be an indispensable handbook for special students of the nervous system, and an invaluable work of reference to those who wish a concise and modern account of its structure. B. L.

A Diabetic's Own Cook Book. By Stella H. Lyons. With a Foreword by Logan Clendening. Pp. 94. New York: Alfred A. Knopf, 1932. Price, $2.00.

The book is a compilation of menus, recipes and tables of food values. The author is a diabetic who has incorporated into this book her experience with the preparation of food and arrangement of diets. One object of the book is to relieve the patient of the use of the scale and metric measurements. She has in most instances used both metric measurements and their equivalents in household measures. There are, however, menus where only household measurements are employed. This book will be helpful to patients whose physicians are satisfied to have the quantities of food measured with a teaspoon, tablespoon and cup. L. J.

Causation, Diagnosis and Treatment of Cancer. The Beaumont Foundation Lectures, Series No. 10. By James Ewing, M.D., Professor of Pathology, Cornell University Medical College. Pp. 87. Baltimore: The Williams & Wilkins Company, 1931. Price, $1.00.

From among the welter of newly published books there occasionally arises one which is outstanding. To make the acquaintance of such a book renews one's faith in the value of the printed page.

In this small book is condensed and evaluated our present knowledge of cancer. Throughout the text there are erected for the guidance of those who have eyes which see many sign posts mapping the paths which lead to the future solution of the problem of cancer.

No student or practitioner of medicine can afford not to know this book.

G. W.

A Bibliography of the Honorable Robert Boyle, Fellow of the Royal Society. By H. F. Fulton, M.A., (Oxon), Formerly Fellow of Magdalen College, Oxford. Pp. 170; illustrated. Oxford: University Press, 1932.

From previous works of Fulton's such as "Physiology" in the Clio Medica series, it was so obvious that Robert Boyle was one of his favorites that it is no surprise to see this beautiful bibliography. The plan of the volume is as follows: After the 9-page Preface with some interesting details about Boyle's life and on various bibliographical details, 42 of Boyle's separate works are treated in detail under 197 items. Contributions to other works (mostly the Philosophical Transactions) are followed by the various editions of his collected works, with a final chapter of over 100 items of elegies, biographies and commentaries. In the appendices are given lists of Boyle's Lecture Sermons since 1692 and of the Robert Boyle Lectures (founded 1892). While obviously a book chiefly of use as a record, and disclaiming any attempt to deal with Boyle's position in science, it contains, concealed in its explanatory paragraphs, much that is of interest to the amateur of the history of science.

E. K.

Practical Treatment of Skin Diseases. By Eduard Ahlswede, M.D., New York and Hamburg, Formerly Assistant Physician, University Skin Department, Direction of Professor Unna, Eppendorf Hospital, Hamburg, etc. Pp. 770; 77 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $12.00.

This interesting work is a manual of dermatologic treatment, essentially a formulary containing much valuable information and numbers of prescriptions. It will be of even greater service to the newer generation of dermatologists in supplying them with many of the time-honored tools of the specialty than it will be to the practitioner. The arrangement of the topics is alphabetical under disease names, the illustrations largely devoted to physiotherapeutic apparatus. In the effort to make the work inclusive, such subjects as scarlet fever, which might better have been left to medical texts, have been introduced. The extended use of proprietary and personal names for preparations without adequate explanation of their meaning is a disadvantage. The work expresses very well the essentially local treatment traditions of dermatologic therapy, the management of constipation in acne, for example, being confined to the essentially archaic jalap and mercurial cathartics. Anti-infection vitamines, liver extract, diet in psoriasis, diet in general as a therapeutic agent receive little or no attention. Many conflicts of opinion find their expression rather in a total elimination of the conflicting viewpoints, as for example in the light therapy of psoriasis rather than in a balanced consideration of the pros and cons. The psychogenous dermatoses, important at the moment in our high-tension American life, receive one page with the advice that they be referred to a neurologist. Notwithstanding these easily recognized deficiencies, this book is a useful one which should materially increase the versatility and elegance

of the dermatologist's approach to many even commonplace treatment problems. There are no illustrations of cutaneous diseases, and there is no bibliography so that the tyro and the researcher should not confuse this with a student's text or a scientific monograph. J. S.

REFLEX ACTIVITY OF THE SPINAL CORD. By R. S. CREED, D. DENNY-BROWN, J. C. ECCLES, E. G. T. LIDDELL and C. S. SHERRINGTON. Pp. 183; 71 illustrations. New York: Oxford University Press, 1932. Price, $3.25.

IN the 6 years that have elapsed since the publication of Fulton's excellent monograph, much light has been thrown on the mechanisms of reflex action. No laboratory has contributed more to that end than that of physiology at Oxford. A review of the subject by Sir Charles Sherrington and his colleagues is to be welcomed as the filling of an urgent need by those best qualified for the task. Within the limits of 165 pages of text, it might seem impossible to write more than an elementary primer or perhaps an analysis of some of the most recent advances in such a field. The book is neither of these things. It is a lucid synopsis of virtually all that is known about the subject today. So skillfully has Dr. Liddell correlated the contributions of his co-authors, that the reader unfamiliar with the material might well mistake it for the work of a single hand. Both for him and for one conversant with all of the 209 papers which comprise the bibliography, the little volume holds compact several hours of delightful and stimulating reading. G. McC.

CEREBRAL INJURY IN NEW-BORN CHILDREN CONSEQUENT ON BIRTH TRAUMA; WITH AN INQUIRY INTO THE NORMAL AND PATHOLOGIC ANATOMY OF THE NEUROGLIA. By ERIK RYDBERG. Pp. 247; 49 illustrations. Copenhagen: Levin & Munksgaard, 1932.

THIS monograph is divided into two parts: one dealing with the anatomy of the neuroglia in the infant brain and the other with the study of the brain after birth trauma. Particular attention is given to the characteristics of the matrix tissue, a portion of the infant brain which requires still further study. Rydberg differentiates unorthodoxly between small and large spongioblasts. He comes to the conclusion further that the microglia is of ectodermal rather than of mesodermal origin (as proved by Hortega), and that it is derived from the ependyma mainly, but in part also from the vascular elements or the leptomeninges. In opposition to the present concept of neuroglia, he favors the view that "the astrocytes appear as widely ramified cells with an extensive plexiform extension of the expansions, and a dense reticulum becomes visible which is connected with the expansions of both the astrocytes and the oligoglia cells, forming a direct continuation of them." Rydberg takes up also the question of the identity of the embryonic fat granule cells. He found that the fat was mostly extracellular, surrounding astrocytes, oligodendroglia and microglia; rarely the microglia, and presumably had to do with myelinization.

The matrix tissue needs study and the author has made a serious attempt to unravel its characteristics. However, his conclusions concerning the microglia and the glial reticulum cannot be accepted without better proof; the contrary evidence is too convincing.

The second portion of the monograph deals with a study of 100 fetuses born at term or within 10 days after birth. Gross hemorrhages were

found in 58 cases, meningeal in 56, cerebral in 28 and subependymal in 11. Rydberg attributes the hemorrhages to "a primary circulatory obstruction in the brain, due to local brain pressure." Compression of the head causes an increased intracranial pressure, which is followed by a secondary rise in blood pressure. If a sudden fall in intracranial pressure causes a marked difference between intravascular and extravascular pressure, hemorrhage results. "This may happen at the moment of the cessation of a pain, if the fetal blood pressure is raised to a high level."

The monograph is written in English. It is well illustrated. The first portion seems more valuable than the second. The conclusions reached by the author are open to question. B. A.

Recent Advances in Pathology. By Geoffrey Hadfield, M.D., F.R.C.P. (Lond.), Professor of Pathology in the University of London; Pathologist to the Royal Free Hospital, and Lawrence P. Garrod, M.A., M.B., B.Ch. (Camb.), M.R.C.P. (Lond.), Bacteriologist and Lecturer in Bacteriology, late Demonstrator of Pathology, St. Bartholomew's Hospital. Pp. 392; 67 illustrations. Philadelphia: P. Blakeston's Son & Co., 1932. Price, $3.50.

The "Recent Advances" series, which now covers 25 subjects, has received here one of its most important additions, forming with "Surgery," "Children," "Bacteriology" and "Chemotherapy" larger books than the rest of the series. Of the 15 chapters "The Reticulo-endothelial System," "The Ductless Glands," 4 on cancer research, 2 on the cardiovascular system and 2 on Bright's disease are the most important. It is obvious that the authors have achieved their main purpose of presenting "recently acquired knowledge of disease processes in a form useful to the student of medicine." In fact, their success raises the question as to whether this is not a better "follow-up" method than the costlier loose-leaf systems that are more in vogue in this country. While occasional slips are noted, such as the confusion of open and closed circulation in the spleen (p. 29), the information is accurate and the material well chosen. The American literature is well represented—possibly somewhat at the cost of the German—and the photomicrographic illustrations really illustrate. The British ability for sane evaluation and clear elucidation has borne good fruit in this useful volume. E. K.

Italian Medicine, Vol. 6 of Clio Medica. By Arturo Castiglioni, M.D., Professor of the History of Medicine, Royal University of Padua, Italy. Translated by E. B. Krumbhaar, M.D., Professor of Pathology, University of Pennsylvania. Pp. 134; 11 illustrations. New York: Paul B. Hoeber, Inc., 1932. Price, $1.50.

In this small volume, the author has made easily available to the busy practitioner and student of medicine many interesting trends in the development of medical thought in Italy which heretofore were only to be found, at the expense of a considerable amount of labor, scattered throughout the voluminous literature of medical history. The history of Italian medicine is the framework of medical history in general and is obviously too vast and too complex to be concentrated in all its interesting details in one small volume. The author, one of the leading medical historians of modern times, has selected the most important and significant facts in each period and has presented them in a readable and concise form with none of the earmarks of the choppy outline and none of the characteristics of the pedantic treatise. The origin of Italian medicine in Southern Italy

is traced from the philosophic schools of Greece and followed through the schools of Monte Cassino and Salerno, the Universities, the Renaissance and so on to modern times. Throughout the book, the development of medicine is skillfully correlated with social and political history, and the evolution of art and literature. A. C.

LEONARDO DA VINCI. By PROF. DR. SIGMUND FREUD, LL.D. (Univ. of Vienna). Translated by A. A. BRILL, PH.B., M.D., Lecturer in Psychoanalysis and the Psychosexual Sciences, Columbia University. Pp. 130; illustrated. New York: Dodd, Mead & Co., 1932. Price, $3.00.

A CONTINUATION of Freud's "valiant effort" to solve the problem of sexuality, this book aims to explain Leonardo's inexplicable genius, at the same time giving a clinical demonstration of the author's psychosexual theories.

According to Scognamiglio, Leonardo once wrote about his childhood as follows: "It seems that it had been destined before that I should occupy myself so thoroughly with the vulture, for it comes to my mind as a very early memory, when I was still in the cradle, a vulture came down to me, he opened my mouth with his tail and struck me a few times with his tail against my lips." From this scene, which Freud regards as a phantasy of later life transferred to infancy, the author says that he will attempt to fill in the gaps of Leonardo's life story by analysis of the phantasy. With his well-known ability to find sexual explanations, the author translates the phantasy erotically, the vulture's tail, coda, being a substitutive designation of the male member, suggesting the act of *fellatio*. This is, however, dismissed by him as a natural occurrence of harmless origin, reminiscent of nursing. On similar grounds, the vulture is thought to represent the mother, as it does in Egyptian mythology, whose vulture-headed motherly deity, Mut, is suggested as related to "Mutter." In the writings of the Church Fathers in connection with Virgin birth, vultures were regarded as all females (impregnation occurring by the wind); hence Leonardo, the illegitimate child, formed the phantasy of the vulture-child with a mother but no father. On grounds of such solidity the author feels he can fill in a gap in Leonardo's childhood, to show that his reception in his father's house (known to be before the age of 5 years) must have been *after* the decisive years of his "infantile sexual investigation" when he formed his mother-cherishing, father-missing complex. Further examples of the author's expressed intention to fill in gaps, however, are not apparent on perusal of later pages.

Through the erotic relations to the mother, the author reasons that Leonardo became homosexual, giving as evidence his love for fine apparel and his good-looking male pupils, though he admits that proof is quite lacking. Later he states that "Sexual repression caused him to sublimate his libido into a thirst for knowledge, which conditioned his sexual inactivity for his entire later life." Even the author admits that two of Leonardo's characteristics remain unexplained, "First, his particular tendency to repress his impulses, and second, his extraordinary ability to sublimate the primitive impulses."

To those who enthusiastically follow this modern pioneer of sexual philosophy, this interpretation will doubtless be sufficient and absorbing. The cover advertisement even speaks of it as one of the outstanding achievements in the field of psychology. The larger number of readers, unsympathetic and critical, will find that it confirms their skepticism if their curiosity leads them to consider it at all. Few, indeed, will be converted by such phantastical, far-fetched and often loose and illogical reasoning.

E. K.

SURGERY OF THE CHEST. By GEORGE F. STRAUB, M.D., F.A.C.S. Pp. 475; 341 illustrations, including 68 color plates. Springfield, Ill.: Charles C Thomas, 1932. Price, $10.50.

EXCELLENT chapters on the history of chest surgery and the principles of the physiology and surgical physiopathology of the chest precede discussion of the Roentgen ray and bronchoscopy in the diagnosis of intrathoracic lesions. Two chapters, each adequately illustrated, show the general principles of the technique of intrathoracic operations, including anesthesia. His description of the operative treatment of tuberculosis shows a wide experience with the method. In the discussion of acute empyema he does not mention the modern methods of tidal drainage which are now in common use in this country. Very little space is given to the treatment of lung abscess and bronchiectasis. An excellently written chapter describes the surgery of the heart. Surgery of the mediastinum is treated more completely than in most other one-volume books. The author illustrates profusely the various operative methods, drawing largely from the German literature. The final chapter in the book is devoted to the surgical treatment of angina pectoris and asthma by sympathetic nerve ganglion resection.

The book represents a valuable addition to the literature on the surgery of the chest. It is up to date in most particulars and is extremely well illustrated. No references are quoted directly but a bibliography is included before the index. The author writes with an easy style and the printing and binding are in excellent taste, all of which combine to recommend the work to those interested in obtaining a knowledge of this branch of surgery.

L. F.

CANCER: WHAT EVERYONE SHOULD KNOW ABOUT IT. By JAMES A. TOBEY, DR. P.H. With Introduction by JOSEPH COLT BLOODGOOD, M.D., and H. L. MENCKEN. Pp. 323; 17 illustrations. New York: Alfred A. Knopf, 1932. Price, $3.00.

THIS book, prepared to assist in the campaign for the "Control of Cancer," is intended chiefly for the general public. In the campaign whose foundation stone is "come early and hope to be cured," we may have arrived at the point where its evaluation as a means of diminishing the incidence of cancer can soon be determined.

In criticism of the book it might be said that its size and cost may lessen its popularity, that it is discursive, carrying the reader into many entertaining but unnecessary by-paths, and that it gives the impression of inconsistency and contradiction by overemphasizing the curability of a disease shown afterward to be really very fatal.

J. McF.

LA MALADIE DE BOECK. By A. KISSMEYER, Médécin de l'Institut Finsen. Preface by DR. J. DARIER. Pp. 147; 67 illustrations. Copenhagen, Levin and Munksgaard, 1932.

THE protean morbid anatomic changes on the skin and histology are covered exhaustively in an authoritative manner. The newer information about bone lesions is particularly needed and welcome. The author stems the current trend to regard sarcoid as a tuberculid, criticizing the validity of tubercle bacillus findings, and even hinting at such other granulomas as leprosy as a causative factor.

F. W.

THE CAMBRIDGE MEDICAL SCHOOL. By SIR HUMPHRY DAVY ROLLESTON, BART., G.C.V.O., K.C.B., M.D., HON. D.SC., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, etc. Pp. 235; illustrated. New York: The Macmillan Company, 1932. Price, $5.00.

To those who wish to follow the thread of British medical education through the tangled skein of their medical progress this book will prove more helpful as well as vastly more entertaining than the more direct educational statements. Written in the author's well known charming style and with full regard for the principle that personalities are more intriguing to the average reader than abstractions or pedagogical events, the book first tells the general story of the Cambridge medical and then gives short accounts of its various departments. To the historically minded the earlier story will perhaps prove the more interesting, though the larger part of the book contains lengthier chapters about the various departments, especially the seven preclinical chairs, that permit more adequate and satisfactory treatment. Lists of the holders of the various chairs are valuable both for reference and as showing how great may be the influence of one mind, both in quality and in the number of years that it is exerted. The well chosen illustrations complete the satisfaction with which one handles this volume. E. K.

BUILDERS OF AMERICAN MEDICINE. Being a Collection of Original Papers read before the VICTOR C. VAUGHAN Society of the University of Michigan Medical School. Pp. 243; illustrated. Ann Arbor: George Wahr, 1932.

THE portrayal of 12 noted American physicians in this book is in itself a real addition to American medical history; but it possesses still further importance as an example of the constructive interest that medical school seniors can exhibit. The Victor C. Vaughan Society is to be congratulated not only on the historical acumen and literary ability shown by the authors of the 12 chapters here selected from their fortnightly meetings, but also on its successes in outlining to other medical students a valuable approach to the fascinations of medical history. E. K.

BOOKS RECEIVED.

NEW BOOKS.

A Handbook of Experimental Pathology. By GEORGE WAGONER, M.D., Associate in Pathology, and R. PHILIP CUSTER, M.D., Associate in Research Pathology, The School of Medicine, University of Pennsylvania. Pp. 160; 22 illustrations, various tables and charts. Springfield, Ill: Charles C Thomas, 1932. Price, $4.00.

Clinical Gynecology. By C. JEFF MILLER, M.D., Professor of Gynecology, Tulane University School of Medicine; Chief of the Department of Gynecology of Touro Infirmary, etc. Pp. 560; 134 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $10.00.

Synopsis of Gynecology. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor of Clinical Gynecology, Washington University Medical School, etc.; and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Pp. 227; 110 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $2.75.

Clinical Laboratory Manual for Nurses and Technicians. By SISTER ALMA, Chief Laboratory Technician and Instructor of Nurses at St. Thomas Hospital, Akron. Pp. 159; 55 illustrations. St. Louis: The C. V. Mosby Company, 1932. Price, $1.75.

Antony van Leeuwenhoek and his "Little Animals." By CLIFFORD DOBELL, F.R.S., Protistologist to the Medical Research Council, London; Foreign Member of the R. Accádemia dei Lincei, Rome; Sometime Fellow of Trinity College, Cambridge. Pp. 435; illustrated. New York: Harcourt, Brace & Co., 1932.

Children's Tonsils In and Out. By ALBERT D. KAISER, M.D., Associate Professor of Pediatrics, University of Rochester Medical School, etc. Pp. 307; 25 figures. Philadelphia: J. B. Lippincott Company, 1932. Price, $5.00.

Alcohol and Man. Edited by HAVEN EMERSON, M.D., De Lamar Institute of Public Health, Columbia University. Associate Editors: HENRY A. CHRISTIAN, M.D., and REID HUNT, M.D., Harvard University; ARTHUR HUNTER, LL.D., F.A.C.S., New York Life Insurance Company; CHARLES C. LIEB, M.D., Columbia University; WALTER R. MILES, PH.D., Yale University; ERNEST G. STILLMAN, M.D., Rockefeller Institute for Medical Research. Pp. 451; illustrated with tables. New York: The Macmillan Company, 1932. Price, $3.50.

Causation, Diagnosis and Treatment of Cancer. The Beaumont Foundation Lectures, Series No. 10. By JAMES EWING, M.D., Professor of Pathology, Cornell University Medical College. Pp. 87. Baltimore: The Williams & Wilkins Company, 1931. Price, $1.00. For review see p. 116.

Publications of the Committee on the Costs of Medical Care: No. 19. University Student Health Services. A Study of Organization, Services Rendered, and Costs in Cornell University, Yale University, the University of Michigan, the University of Minnesota, the University of California, and Oregon State Agricultural College. By DON M. GRISWOLD, M.D., DR. P.H., and HAZEL I. SPICER. Pp. 114; illustrated with tables. *No. 20. A Community Medical Service Organized Under Industrial Auspices in Roanoke Rapids, North Carolina.* By I. S. FALK, PH.D., DON M. GRISWOLD, M.D., DR. P.H., and HAZEL I. SPICER. With Reports on Certain Phases of the Organization by DAVID RIESMAN, M.D., SC.D., and GEORGE P. MULLER, M.D. Pp. 105; illustrated with tables. Chicago: The University of Chicago Press, 1932. Price, 90 cents each.

Practical Obstetrics. By P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College; Chief Obstetrician, Jefferson Medical College Hospital. Assisted by THADDEUS L. MONTGOMERY, M.D., Associate in Obstetrics, Jefferson Medical College. Pp. 730; 516 illustrations, including 21 colored plates. Philadelphia: F. A. Davis Company, 1932. Price, $8.00.

Transactions of the American Otological Society, Inc. Vol. XXII. Sixty-fifth Annual Meeting, Atlantic City, May 17 and 18, 1932. Published by the Society, 1932. Pp. 376; illustrated.

NEW EDITIONS.

Injuries of the Eye. By HARRY VANDERBILT WÜRDEMANN, M.D., SC.D., F.A.C.S., Colonel, Medical Reserve Corps; Flight Surgeon, Air Corps, U. S. Army, etc. Pp. 900; 236 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1932. Price, $13.50.

The second edition of this book is a complete treatise on injuries of the eye and their treatment. The more recent original literature is included.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,
AND
JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Quantitative Aspects of Iron Deficiency in Hypochromic Anemia: The Parenteral Administration of Iron.—During the past few years a certain amount of information has been derived from various studies which indicate that many forms of hypochromic anemia depend chiefly on deficiency of iron. In the present study of HEATH, STRAUSS and CASTLE (*J. Clin. Invest.*, 1932, **11**, 1293) two purposes were undertaken; first, to compare the doses of iron given parenterally with that given by mouth, and, second, to determine the fate of iron administered parenterally in order to establish a quantitative basis for the better knowledge of this type of deficiency. For the purpose of the investigation, 17 patients with hypochromic anemia were studied most completely. It was found that 1000 mg. of metallic iron given orally is approximately equivalent, from the point of view of the building of blood, to 32 mg. of iron given parenterally. The amount of iron given in this way represented quite closely the amount of iron gained in the circulating hemoglobin and is used in the building of new hemoglobin. For several reasons the authors think it inadvisable to give such large doses of iron parenterally and state that it is undesirable to give the iron this way rather than by mouth. They conclude from these studies that certain types of hypochromic anemia are dependent upon a deficiency of iron which prevents adequate hemoglobin formation.

Relationship Between Acute Liver Injury Induced by Alcohol, Retention in Plasma of Phenoltetrachlorphthalein and Elimination of Phenolsulphonephthalein.—Several months ago in this section was recorded some observations which have been made on the effect of liver injury and the elimination of phenolsulphonephthalein. In this connection it was shown that animals which were given alcohol, which presumably injured the liver, had a high elimination of phenolsulphonephthalein and that despite a concomitant nephritis in an occasional animal. MACNIDER (*Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 78) has continued his studies on this problem and has reported upon a series of animals who were

kept in a state of semialcoholic anesthesia as a result of the repeated introduction from time to time of 10 to 15 cc. of 40 per cent of ethyl alcohol for 12 hours. Eight experimental animals were used and 4 controls, in order to study if there was any relationship between the percentage of retention and rate of disappearance of phenoltetrachlorphthalein from the plasma and the percentage of phenolsulphonephthalein elimination during acute liver injury. It was found that in the control animal elimination of phenolsulphonephthalein was 66 per cent in a typical observation and the concentration of phenoltetrachlorphthalein was 8 per cent. An excised liver specimen was entirely normal. A sample experiment with an experimental animal showed a phenoltetrachlorphthalein concentration of 16 per cent and a retention of 7 per cent of the dye at the end of an hour. Elimination of phenolsulphonephthalein was 83 per cent. The biopsy of the livers of these dogs exhibited marked edema, failure of the nuclei to stain normally and the presence of certain amounts of stainable lipoid material which involved chiefly the periphery of the lobules. By this method of experimentation, using phenoltetrachlorphthalein, there was shown to be a definite relation between the degree of liver injury and renal elimination of phenolsulphonephthalein.

SURGERY

UNDER THE CHARGE OF

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Water Balance.—The fluid requirements of the surgical patient has within recent years attracted the attention of the surgeon. The patient may be unable to swallow fluids as the result of a lesion of the esophagus so that dehydration results from mere fluid restriction. Such dehydration if not too extensive can be corrected by the simple ingestion of water (AUSTIN and RAVDIN, *Trans. Coll. Phys., Phila.*, 1931, **53**, 10). On the other hand, besides simple restriction there may be a marked loss of fluid either by vomiting or from a fistula. Under such circumstances there is not only fluid loss but a loss of salt at the same time. In the acute abdominal crises of an obstructive or suppurative character, in extensive superficial burns, and in fistulæ of the gastrointestinal tract, the maintenance of an adequate fluid intake and salt balance becomes a matter of paramount importance (ORR, *Am. J. Surg.*, 1932, **18**, 279). Not only is the loss of fluid from vomiting, denuded areas, and fistulæ of importance, but the loss of fluid through the skin and lungs is equally important. WILEY and NEWBURGH (*J. Clin. Invest.*, 1931, **10**, 689) have made comparisons of the sources of supply and routes by which fluid is lost from the body. These authors studied

the relationship between the environment and the basal insensible loss of weight. They were able to calculate the insensible loss of water and found that in the case of the nude subject, the heat lost by the vaporization of water increased with environmental temperature and decreased with increasing humidity. With a clothed individual changing humidity did not affect the amount of heat vaporized, but this value was still influenced by temperature. In a subsequent study NEWBURGH, WILEY and LASHMET (*J. Clin. Invest.*, 1931, **10**, 703) found that the water vapor in a 24-hour period carried with it 24 per cent of the total heat production. Later WILEY and NEWBURGH (*J. Clin. Invest.*, 1931, **10**, 723) showed that the mechanism which regulates the water content of even the normal individual is extremely labile. These authors have shown that the common clinical method of studying the water exchange by comparing the fluid ingested with the urine and other easily calculated output is erroneous. The insensible loss of water through the skin and lungs was often greater than the loss of fluid through the kidneys. The water of oxidation varied from 30 per cent to 75 per cent of the water eliminated in the urine. From their studies they conclude that none of the factors involved in the water exchange can be omitted if any accurate knowledge of water balance is to be obtained. COLLER and MADDOCK (*J. Am. Med. Assn.*, 1932, **99**, 875) on the basis of Wiley and Newburgh's work have studied the insensible loss of fluid in surgical patients. In a study of 18 patients these authors found that during operation and a 4-hour postoperative period the average loss of fluid amounted 1000 cc. Of this amount by far the greater amount (700 cc.) resulted from loss by perspiration and by the insensible loss. These studies indicate in a striking manner the strain placed on the patient's water stores during and after operation. A series of papers by GAMBLE (*New England J. Med.*, 1929, **201**, 909), HADEN and ORR (*New York State J. Med.*, 1930, **30**, 1161) have stressed the importance of the salt loss which is usually associated with fluid loss in surgical patients. The major ions lost are sodium, chlorid and bicarbonate. The persistent loss of these ions results in a disturbance of the acid-base balance. Whether the final condition is one of alkalosis or acidosis depends on the degree to which acid or base ions are lost. With either condition there may be an associated ketosis. Simple hemoglobin or hematocrit estimations are useful methods in determining the degree of dehydration beyond the examination of the texture of the skin and mucous membranes and the urinary output. Valuable also are the methods for studying serum protein. The PAGE and VAN SLYKE method (*J. Am. Med. Assn.*, 1932, **99**, 1344) is simple and probably much more accurate than is the determination of serum protein by the refractometer. Recently DOLCH and POECHMULLER (*Hoppe-Seyler's Zeitsch.*, 1931, **195**, 28) have described a new method for determining the water in the blood and this may prove a valuable addition to our other methods of determining fluid requirements. DRAKE, MARSH and GAMBLE (*Am. J. Dis. Child.*, 1930, **40**, 705) have in a very interesting article shown that, in treating dehydration in which there is an associated disturbance of the acid-base balance, it is more important first to correct dehydration before attempting to correct blood reaction. In fact, in the majority of instances the correction of the dehydration and salt loss will at the same time correct the acid-base disturbance.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

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Fever Therapy of Neurological Diseases With Pyrifer.—Presenting a critical analysis of the results obtained in 130 patients who were observed for from 1 to 4 years after treatment with pyrifer, out of a total of 220 patients to whom this agent was administered, MANDL and SPERLING (*Med. Klin.*, 1932, **28**, 620) submit the following conclusions: Pyrifer constitutes no advance in the therapy of progressive general paralysis. Although one can produce complete remissions, these are, however, not lasting. The agent is of value in these cases only as a substitute for malaria or relapsing fever therapy, when contraindicated or impossible. The best results from the use of pyrifer are obtained in tabes dorsalis. In those cases, however, where there are serious changes in the spinal fluid, malaria therapy is preferable. Pyrifer treatment is contraindicated in cases of tabes dorsalis of the severe atrophic-atactic forms and in the presence of optic atrophy. The results are promising in cases of cerebral spinal syphilis which are not of long duration and which do not show irreparable damage. The influence of pyrifer on the spinal fluid in general paralysis is less profound and less lasting than is that of malaria treatment. It more nearly approaches malaria treatment, however, in its influence upon the spinal fluid in tabes and cerebrospinal lues. Pyrifer acts favorably upon the individual recrudescences of multiple sclerosis and perhaps may ward off progress of the disease for a few years, but it is not capable of preventing new recurrences and it is contraindicated in the very acute ones and useless in the severe chronic forms. The results of its use are questionable in Parkinsonism and schizophrenia. The best results are obtained in the syphilitic lesions when pyrifer treatment is combined with the administration of neoarsphenamin. If the proper technique be employed and the indications and contraindications be observed, the use of pyrifer is without danger.

Ephedrin Treatment of Narcolepsy.—In view of the general failure of all previous attempts to treat narcolepsy and of the recent favorable results reported from the administration of ephedrin, COLLINS (*Ann. Int. Med.*, 1932, **5**, 1289) employed it in 2 patients under conditions of well-controlled observation. He reports complete control of the symptoms in both patients which control became manifest almost immediately after the beginning of the therapy. In both instances, however, it was necessary to place the patient upon continued administration of the drug in order to maintain control. He states that

the best results are obtained by administering the drug orally, 3 times a day, in doses of 0.025 to 0.05 gm. ($\frac{3}{8}$ to $\frac{3}{4}$ grain). The best times for administration seem to be at about 8 A.M., noon and 4 P.M. The time of the latter dose is especially important in order to avoid overstimulation of the patient which may persist into the normal sleep period if the drug be administered later in the day. It is wisest to begin with the smaller dose and to increase until the minimal effective dose is determined for each individual patient. Larger doses than the maximum stated seem occasionally to be required but were not necessary in either of the patients who were the subjects of these observations.

On the Action of the So-called Circulation Hormone Upon Vascular Tonus.—SCHRETZENMAYR (*Ztschr. f. Kreislaufforsch.*, 1932, **24**, 225) conducted a series of comparative experiments upon intact animals for the purpose of studying the actions upon the tone of the vessels of the following so-called hormones: eutonon, myoston, lakarnol, padutin; and of comparing them with the actions of pure adenosin phosphate. He finds that the four so-called hormones are similar in their actions to the extent that these actions are exerted upon the periphery where they produce a greater or lesser degree of reduction in the tone of the arteries in the extremities, the intestinal tract and the kidney. Both quantitative and qualitative differences occur, however, in the actions of these substances. Eutonon can be shown pharmacologically to exert three distinct actions—one like cholin, a sympathomimetic action and a direct action producing relaxation of smooth muscle. Whether these actions are due to a single substance or to different substances contained in eutonon has not been established, but the latter interpretation seems the more probable since no one substance so far known possesses these three dissimilar properties. Myoston and lacarnol resemble adenosin phosphate in their capacity to diminish vascular tone. Myoston, however, also contains a sympathomimetic component. Padutin on the other hand exerts a direct muscular depressant action on the arterioles. Both adenosin phosphate and the several hormone preparations are capable of promptly antagonizing the disturbances in cardiac rhythm which are produced by gynergen, barium and calcium. From these comparative studies the author feels that future therapy of the spastic disorders of the bloodvessels will be concerned chiefly with the use of adenosin phosphate rather than of the so-called circulatory hormones.

The Treatment of Thyrotoxicosis With Hydrofluoric Acid.—GORLITZER (*Med. Klin.*, 1932, **28**, 717) reviews the well-known depressant influence of iodin upon the basal metabolism and reports his own experiments and those of others which show that all of the halogens exert a similar influence, fluorin being by far the most active. He also presents evidence to show that fluorin can be absorbed through the unbroken skin in the form of dilute solutions of hydrofluoric acid. On the basis of these considerations, the author has treated a group of patients suffering from thyrotoxicosis by a series of baths in dilute hydrofluoric acid. The baths were given at an average temperature of 30° C. for a duration of 20 minutes and contained 30 cc. of concentrated hydrofluoric acid in 200 liters of water. Slight variations were made in the

temperature of the baths to suit individual need. No harmful results whatsoever and no discomfort were produced by these baths. The number of baths employed varied for different patients between 4 and 20. In all 24 patients were treated in this manner and the effects of the treatment were controlled both by careful recording of the clinical signs and by changes in the basal metabolism and the body weight. All patients derived considerable improvement from the treatment, many of them having the basal metabolism brought down in a significant manner, but in no instance to normal. In this latter group of patients there was generally also a significant gain in weight. The effects of the treatment seemed to be fairly lasting as determined by adequate follow-up studies. In a few of the patients the baths alone were insufficient to bring about sufficient measure of clinical improvement and reduction of basal metabolism and in these operative procedures were undertaken after which repetition of the baths proved effective. The author cautions concerning the difficulty of handling hydrofluoric acid in its concentrated form and warns that the bath tub must be lined with an impervious layer of rubber in order to prevent the action of acid upon the tub wall.

PEDIATRICS

UNDER THE CHARGE OF

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Hemophilia.—Birch (*J. Am. Med. Assn.*, 1932, **99**, 1566) studied 35 cases of hemophilia. The ages ranged from the newborn to 52 years. Of these cases 7 were sporadic, while 28 had a definite family history. The histories of 20 families were traced. These consisted of from 4 to 7 generations. An analysis of these histories shows that persons with hemophilia have more daughters than sons, while transmitters have more sons than daughters. Over 71 per cent of the transmitters' sons had hemophilia. Only 10 to 15 per cent of the transmitters' daughters had at least 1 normal son and no hemophiliac sons. Of the hemophiliac daughters, only 3 to 7 per cent had at least 1 normal son and no hemophiliac sons. Nineteen patients had been receiving ovarian therapy for more than 6 months; 9 of these showed a good response, and 9 showed definite but less marked improvement, while the condition of 1 remained unchanged. The response was both general and specific. The general improvement was shown by an increase in weight, hemoglobin and vitality. The specific response was shown by a decrease in number and severity of hemorrhages and a lowering of the coagulation time. The prolongation of the coagulation time in hemophilia is due to increase in the resistance of the blood platelets, for when this resistance is overcome the blood clots in normal time. The blood of a person with hemophilia is morphologically normal. The red cells and hemoglobin may show a secondary anemia, the degree of which depends on the extent and recency of hemorrhage. The white

cells, especially the polymorphonuclear neutrophils, are increased following confined hemorrhages. The thrombocytes are present in normal number, and their morphology does not differ from the normal. The resistance of the thrombocytes is greatly increased, and when this resistance is overcome the blood clots in normal time. This shows that the prolongation of the coagulation time is due to the increased resistance of the blood platelets. If the clotting time of the blood is in excess of 1 hour, the red cells settle to the bottom, leaving blood plasma above. In a general way, the sooner sedimentation begins, the longer the clotting time will be. Roughly speaking, the severity of the hemophilia is in direct proportion to the length of the clotting time. In 1 patient with a serious hemorrhage the coagulation time was in excess of 45 minutes. Patients are relatively safe if the coagulation time does not exceed 1 hour.

Congenital Syphilis.—Atlee and Tyson (*Am. J. Dis. Child.*, 1932, **44**, 718) followed 107 babies of syphilitic mothers in their clinic for varying lengths of time. The condition was checked by studies of the blood and by clinical examination. Some of these babies received antisyphilitic treatment. Some babies were not considered as being in need of antisyphilitic treatment or were not treated because of poor cooperation of the parents. In analyzing the result of treatment it was found that in not 1 infant that received at least 1 full course of injections, with regular attendance at the clinic, did any signs or symptoms, serologic or clinical, of congenital syphilis become manifest during the period of observation. The few babies developing symptoms or showing a 4+ Wassermann reactions during their first year had received little or no treatment, and their attendance at the clinic had been irregular. The general condition of the patients followed, when last seen, were extremely good in the great majority of instances. In a few babies whose mothers failed to follow the dietary instructions rickets had developed. There was 1 case in which it was interesting to note that a negative Wassermann should not be relied on as a proof of cure unless corroborated by other data. A greater number of patients than presented in this series must be studied in order to prove the point that is emphasized in this presentation. This is that this minimum amount of treatment, started immediately after birth, is sufficient to cure congenital syphilis in this symptomless stage, which is probably the equivalent of the early primary stage of the disease. The main objection raised to prolonged treatment of these babies lies in the fact that it is impossible to tell at birth which babies are going to develop the disease and which are going to escape it. Those that would escape it might be injured to a certain extent by the intensive treatment advocated by most syphilographers. The authors' experience is that babies who show definite signs of syphilis at birth do not survive even though treated immediately. They feel that a positive Wassermann reaction of the cord blood is sufficient evidence to warrant early antisyphilitic treatment. On the other hand, they feel that a negative Wassermann reaction of the cord blood in a child whose mother is definitely syphilitic is not sufficient evidence that the baby will escape congenital syphilis, and the treatment should be given. In this way a high percentage of cures will result from treatment continued over a period of 14 weeks.

The Newer Conception of Diphtheria Immunization.—STRONG (*Arch. Ped.*, 1932, **49**, 614) states that all children, excepting those showing decided allergic tendencies, should be given the benefit of active immunization against diphtheria during preschool ages of from 6 months to 6 years without a preliminary Schick test. He recommended the administration of not less than 2 or more than 3 1-cc. doses of diphtheria toxoid or the Ramon anatoxin at intervals of 3 weeks. Children of school age and adults show more local and general reactions to the bacterial protein of toxoid. So that an intradermal test for sensitiveness should be performed before administering the immunizing injections. If evidence of sensitiveness appears within 3 days after the intradermal test, the doses of toxoid should be changed and given 0.1, 0.25, 0.5, 1 and 0.1 cc. of diphtheria toxoid at intervals of 1 week instead of 3. The great susceptibility of the preschool child justifies the elimination of the preliminary Schick test, but it is desirable that this preliminary test be performed on older children, especially in the cities where many children will be found who have acquired an immunity. Among rural children there is a greater susceptibility to diphtheria as evidenced by the greater frequency of positive Schick tests. As argument in favor of the toxoid over the toxin-antitoxin as an immunizing agent it is claimed that the toxoid is from 20 to 30 per cent more effective even in the 2-dose administration. It contains no serum to sensitize to later therapeutic sera. It contains no free toxin, and is more stable and is not affected by freezing. It is believed that many of the difficulties of immunization have been obliterated by this newer development.

DERMATOLOGY AND SYPHILIS

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The Life History of the Treponema Pallidum.—After a thorough analysis of the past and present concepts in regard to the etiology and pathogenesis of syphilis, INGRAHAM (*Am. J. Syph.*, 1932, **16**, 155), while not depreciating the great strides that have been made in the last 30 years, feels that our knowledge of this disease, today, leaves much to be desired. When one considers the long and tedious treatment that is necessary to effect a "clinical cure" even in an early case, and when one realizes, as clinical and pathologic studies have so often pointed out, that a conservative physician of the present generation can guarantee no patient freedom from relapse even after the most

vigorous and prolonged treatment, this notwithstanding the apparent specificity of the arsphenamins for the Treponema pallidum, it becomes obvious that a certain refinement of our present-day methods, were such possible, would not be amiss. It is reasonable to suppose that this improvement would be realized most rapidly through a better understanding of the life history of the microörganism causing the disease. Since Schaudinn succeeded in identifying the Treponema pallidum, in 1905, and Noguchi, 6 years later, apparently obtained pure cultures of the microörganism which were virulent, it has become customary to explain the peculiar characteristics of this disease, such as the long incubation periods, the symptomless latent stages, the almost sterile but none the less destructive tertiary lesions, as some unusual reaction on the part of the immunity mechanism of the host which strives with great difficulty, and often unsuccessfully, to destroy the acclimated spirochete. Such hypotheses are difficult to prove or to disprove. Under the circumstances, it seems worth while to consider the supposition that the spirochete of syphilis may perform some type of a cycle of evolution, especially since it has been proved that the related microörganisms, the Trypanosomata, do so, and since it has been suggested in the cases of certain other of the parasitic genera of the Spirochetaceæ, the Cristispira, the Borrelia, and the Leptospira. The idea here presented is not a new one, for it seems that Schaudinn, before his untimely death in 1906, expressed the belief that his microorganism was, in actuality, a protozoön. McDonagh has been bold enough to describe a complete cycle of evolution on what is, perhaps, insufficient evidence. But numerous observers, following in the footsteps of Meirowsky and Levaditi have demonstrated beyond any reasonable doubt that the Treponema pallidum does possess a granular stage. They have not, however, been able to show conclusively that these granules are virulent, and thus, that they are a portion of an evolutive cycle, though much of their work has been strongly suggestive. While it is, perhaps, unnecessary to state that nothing short of absolute proof of this evasive problem should be accepted, it would seem that further studies with slight modifications of the older techniques might bear worthwhile fruit.

Pemphigus Treatment With Partly Successful Results.—Sulzberger and Wise (*Med. J. and Rec.*, 1932, **136**, 64) report 5 consecutive cases of pemphigus, 3 of which were either cured or markedly improved, 1 died of pneumonia while apparently improving, and 1, after a complete remission, suffered a severe recurrence after an abdominal operation. The type of treatment suggested by the authors is as follows: (1) Expert nursing; (2) many local measures, including potassium permanganate baths, lotions, etc.; (3) large doses of arsenic; (4) daily high colonic irrigations with large quantities of fluid containing either bicarbonate of soda or an iodin preparation; (5) large quantities of vitamin D; (6) salt-poor, protein-low, vitamin-high diet; (7) trichophytin or monilia vaccine or both. No scientific basis for the above therapeutic measures is claimed by the authors, but empirically they seem to promise the best results as yet available.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Statistics on Cancer of the Cervix.—The report presented by PHILIPP (*Zentralbl. f. Gynäk.*, 1932, **56**, 212) from Stoeckel's Clinic in Berlin is based on 446 cases of cervical cancer which were treated between 1923 and 1925. Of this number 40.8 per cent were operable, 19 per cent were borderline and 40.2 per cent were inoperable. The rate of 5-year cures for the group as a whole was 36 per cent but by separate groups it was 57.3 per cent for the operable, 31.7 per cent for the borderline and 16 per cent for the inoperable cases. Of the entire group 131 cases were subjected to surgical operation and 74 (56.5 per cent) remained free from recurrence. Most of these operations were performed by Bumm and Warnekros, who preceded Stoeckel at this clinic. Of this series of operations 109 were in the operable class, with 62 per cent cures, 19 were borderline, with 31.5 per cent cures, and 3 cases were inoperable and all died. Irradiation was given in a series of 315 cases of whom 27.6 per cent remained free from recurrence. By groups this series consisted of 74 operable cases, with 50 per cent cures, 66 borderline, with 32 per cent cures, and 175 inoperable, with 16.6 per cent cures. A comparison of these results with those published from the same clinic for the years 1913–1919 shows that the rate of cure in the old series was 40 per cent for operation compared to the present 56.5 per cent and 15.25 per cent for irradiation as compared to 27.6 per cent in this series. The primary mortality in the 131 Wertheim operations was 8.4 per cent, of which only 5.3 per cent were due to infections. This low rate of fatal infections is probably due to the fact that virulence tests are performed on all carcinomas before operation and those cases which are infected with organisms of high virulence are excluded from operative treatment. Most of the operative cases received postoperative irradiation, but the author is not definitely prepared to say that it has improved the results. In 108 patients the regional lymphatic glands were examined and of 16 cases which showed carcinoma only 2 are free from recurrence as opposed to 58 free from recurrence in a series of 92 in which the glands showed no carcinomatous infiltration. Considering the results of irradiation it was found that the present series showed a curability rate of 50 per cent in operable cases, 32 per cent in borderline and 16.6 per cent in inoperable cases as against 28, 21 and 6 per cent for similar groups in the earlier series. The improvement in these results has been due to improved technique and not to any change in the type of material treated. No advantage was noted in the combination of radium and Roentgen ray over radium alone. A

comparison of the relative cures obtained by irradiation and by operation would seem to indicate that operation gives better results in the early operable cases, but in the borderline and inoperable cases irradiation seems preferable. While statistical summaries are usually very uninteresting, this report, coming from one of the foremost German clinics where there has been an extensive experience in both the operative and irradiation treatment of cervical cancer, shows that their results are excellent for this type of work and have materially improved since the previous report was published.

Cervical Polyps.—When a cervical polyp is found in the course of a gynecologic examination the usual feeling among gynecologists is that an entirely benign lesion is present and that the simple removal of the polyp is all that will be necessary for the complete cure of the patient. That such an opinion is not always justified is stated by FRANKL (*Zentralbl. f. Gynäk.*, 1932, **56**, 1858), of Vienna. In a series of 318 cases he found a carcinoma of the cervix in the tissues adjacent to absolutely benign polyps in 3 instances. Such an experience, he believes, emphasizes the necessity of careful palpation and inspection of the cervix together with exploration of the cervical mucosa with a sound and when broken particles of tissue are recovered, microscopic examination of such tissues. In the presence of a frankly carcinomatous cervical polyp even without associated carcinoma of the cervix, he believes that panhysterectomy is indicated. (The pedicle of the polyp should be examined with especial care.—C.C.N.)

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Uveitis With Dysacousia, Alopecia and Poliosis.—Three cases of severe uveitis resulting in secondary glaucoma, phthisis bulbi, or both, and associated with transitory deafness, alopecia and depigmentation of the skin and hair, particularly of the eyebrows and eyelashes, is reported by RONES (*Arch. Ophth.*, 1932, vol. **7**). In none of these cases was any specific cause of the uveitis found. One of the patients was found to be sensitive to uveal pigment. The fundus was not visible in any of the 3 patients reported by the author. But in several previously reported similar cases depigmentation of the choroid was observed. Depigmentation of the hair and also deafness and alopecia have been reported in association with sympathetic ophthalmia. This fact, taken in connection with the proven sensitivity to uveal pigment in 1 of his cases, suggests to the author that the depigmentation of the

skin and hair seen in patients with inflammatory diseases of the uveal tract is not a chance association, but the result of an anaphylactic reaction affecting the pigmented tissues. These patients have a transient allergy to pigment. No evidence of endocrine dysfunction was found in the reported cases.

Hemorrhagic Retinitis in Vomiting of Pregnancy.—STANDER (*Surg., Gynec. and Obst.*, 1932, **54**, 129) reports 2 cases of hemorrhagic retinitis occurring in patients with pernicious vomiting of pregnancy. The first patient was 5 months pregnant and had been vomiting and losing weight for 2 months. Numerous retinal and subhyaloid hemorrhages of varying size were present in each eye without arterial changes, exudates or edema. Therapeutic abortion was performed 8 days after the onset of hemorrhages, but the patient died 1 day later. Necropsy revealed central necrosis of the liver and numerous patches of necrosis with many hyalin capillary thrombi in the anterior lobe of the hypophysis. The second patient was 4 months pregnant and had been vomiting severely and had lost 30 pounds. Many subhyaloid hemorrhages were present in each eye. Therapeutic abortion was performed immediately after the discovery of the hemorrhages. The patient recovered and most of the hemorrhages had disappeared 3 weeks later at the time of her discharge from the hospital. The changes in the blood and urine in these patients were of the type seen in severe vomiting of pregnancy. No hypertension was present. The hyperglycemia in the first case may have been caused by the lesions in the hypophysis. The hemorrhages in the retina were apparently due to toxic injury to or increase in permeability of the capillary walls. The occurrence of such hemorrhages in the course of vomiting of pregnancy should be regarded as a grave prognostic sign and as an absolute indication for immediate termination of the pregnancy.

Some Remarks on Changes of the Eyeground in Toxemia of Pregnancy.—PILLAT (*Chinese Med. J.*, 1932, **46**, 149) discusses the occurrence of "retinitis of chronic nephritis in pregnancy" and of "retinitis in toxemia of pregnancy." He believes that it is impossible to distinguish the two ophthalmoscopically with any degree of certainty since the picture of each is made up of edema, hemorrhages, punctate exudates, star figures, cotton-wool patches and vascular changes. Four points favor the diagnosis of retinitis in toxemia of pregnancy: The presence of "glassy" edema of the retina, the visibility of folds of the membrana limitans interna, the absence of a typical star figure, the tendency to detachment of the retina. This type of retinitis usually occurs in the last three months of pregnancy with rather sudden onset and heals rather rapidly after the birth of the child. It seldom recurs in subsequent pregnancies. Retinitis of chronic nephritis in pregnancy is apt to occur earlier in the course of the pregnancy, to be chronic and to recur in succeeding pregnancies. The author does not believe that it is necessary to assume a special pregnancy toxin to account for the occurrence of retinitis in pregnancy. Aside from the presence of a recognizable chronic nephritis, it is possible for the woman to have

latent primary or toxogenous hypertension with some damage to the vessel walls which is not recognized by our ordinary tests unless perhaps by examination of the retinal vessels. The strain imposed on these damaged vessels by an ordinary pregnancy might be sufficient to cause lesions of the brain, kidney and retina. Until such latent vessel lesions can be definitely ruled out in all cases, we are not justified in assuming the existence of a retinitis due to circulating pregnancy toxins. The author thinks that optic neuritis and retrobulbar neuritis occurring in the course of pregnancy but not in association with retinitis are due not to the pregnancy proper but to some exogenous factor.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Symptom of Acute Suppurative Sphenoidal Sinusitis Not Previously Described.—MENZEL (*Monatschr. f. Ohrenh.*, 1932, **66**, 81) reports 4 cases of acute sphenoiditis in which lacrimation was a prominent symptom. This is a result of excitation of regional nerves—directly or indirectly—by the inflammatory process in the sphenoid sinus. Menzel urges that widespread observations be made in order to determine more accurately the actual incidence of lacrimation in sphenoiditis.

Pathologic Changes in the Auditory Nerve in Otosclerosis and Their Significance Clinically, Especially With Regard to Paracusis Willisii.—Based upon a histopathologic study of the auditory nerves from four subjects who had suffered from otosclerosis during their life. GRAY (*J. Laryngol. and Otol.*, 1932, **47**, 598) reports many interesting observations and enlightening conclusions: In otosclerosis, the degenerative process begins in the medullary sheath and neurilemma of the cochlear nerve, and later in its axis-cylinder. This process occurs independently of the stapedial fixation or of the bony changes in the labyrinthian capsule—*and it probably precedes both.* The clinical picture of otosclerosis—deafness, paracusis Willisii and tinnitus—is produced for the most part by cochlear nerve degeneration and later only to a minor degree by fixation of the stapes. Gray believes that the diminished secretion of wax in the meatus, the sluggish vasomotor reaction and accompanying diminished sensitiveness of the tympanic membrane, the osseous change in the labyrinth and the degeneration of the cochlear nerve fibers are independent resultants of a common etiologic factor, which is probably to be looked for in the vasomotor arc that controls the nutrition of the structures involved. Incidentally, he thinks that atrophic rhinitis is due to a defective vasomotor mechanism of the nasal reflex arcs.

RADIOLOGY

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The Roentgen Ray Treatment of Gonorrheal Complications in Males.—Deep Roentgen ray therapy in the treatment of the various complications of gonorrhea was studied by LIBERSON (*Radiology*, 1932, **18**, 758) in 119 males over a period of $6\frac{1}{2}$ years. In the order of efficacy, Roentgen ray therapy appears to be uniformly effective in painful heel due to a periosteal spur, may relieve pain of gonorrheal joint complications and has little effect on epididymitis, adenitis or urethritis.

Roentgen Therapy in Bone Metastasis of Carcinoma.—Most of the patients treated by STENSTROM (*Radiology*, 1932, **18**, 741), particularly those exhibiting the osteoclastic type of metastasis, were benefited. Although the improvement was of rather short duration for the group as a whole, it was quite remarkable in some few instances. The Roentgen treatments seemed to be of very definite value in reducing the amount of drugs needed for pain, in getting patients out of bed and in restoring some of them to useful lives for as long as 2 years.

An Original Method of Estimating Kidney Function by Means of the Roentgen Ray in Intravenous Urography.—CARHART (*Am. J. Roent. and Rad. Ther.*, 1932, **27**, 234) has devised a rapid method of estimating the percentage of skiodan eliminated in 30 minutes, and hopes that this will prove to be a direct test of renal function. Six flat-bottom, 20-cc. test tubes are grouped around a similar one at the center. Fifteen cubic centimeters of 2, 3, 4, 5, 6 and 8 per cent solutions of skiodan, respectively, are placed in the outer tubes, forming a scale or meter. In the central tube of the meter is placed 15 cc. of skiodan urine voided by the patient 30 minutes after the intravenous injection. A roentgenogram of the assembled tubes is then made, and the density of the central tube is compared with that of the scale tubes containing the known percentages of skiodan. The quantity of urine passed at 30 minutes is also measured. With these data simple mathematical calculation will determine the total excretion of skiodan in 30 minutes. It is considered that approximately 40 per cent of the skiodan injected should be eliminated at 30 minutes. To be sure that there is no residual urine in the bladder a film is exposed over the bladder area after collecting the 30-minute specimen.

Roentgen Treatment of Agranulocytosis.—Two cases of agranulocytosis successfully treated by Roentgen irradiation are reported by GAGER and SPEER (*Am. J. Roent. and Rad. Ther.*, 1932, **27**, 40). Both cases occurred in young women. In the first case one-third of an

erythema dose applied to the femur produced an immediate amelioration, but several subsequent applications were required for clinical cure. In the second case a single application brought prompt and lasting improvement. The writers consider these results to be an unequivocal demonstration of the specific value of Roentgen irradiation in stimulating the production of granulocytes and of the vital importance of these cells to the body.

Hepatosplenography.—To produce readily visible shadows of the liver and spleen, KADRNKA (*Radiology*, 1932, **18**, 371) has employed thorotrast, which is a 25 per cent solution of thorium dioxid. For intravenous use it is diluted at least 10 times with 5 per cent glucose solution, sterilized by heating, and injected in increasing doses in the course of several days. To determine the patient's tolerance an initial dose of not more than 0.1 grain of thorotrast per kilogram of body weight is given. "After that each dose is increased from 0.1 to 0.5 grain per kilogram of body weight until the desired dose is given, care being taken not to exceed the patient's tolerance." As a rule, a total of 0.8 grain is sufficient to produce an intense shadow. Roentgen observation should be made 24 hours after the last injection. The injections are generally well borne, and the method has appeared harmless over a limited time. "Until it has been used in a larger series of cases, and these have been observed for a longer period of time, it should not be used routinely, especially in young individuals. The indications at present are limited to cases of carcinoma, echinococcus cysts and abscess of the liver and spleen, especially those in which there is a likelihood of subsequent surgical interference." The method should not be used in patients with severe hepatic or splenic insufficiency, especially those in whom there is also renal damage. Excretion of thorotrast is very slow and only after several months is there an appreciable diminution of the shadow density.

A Demonstration of the Lymphatic Drainage From the Maxillary Sinuses.—Ten weeks after injection of a maxillary sinus with lipiodol a roentgenologic examination of the patient was made by PFAHLER (*Am. J. Roent. and Rad. Ther.*, 1932, **27**, 352). At this time a globule of lipiodol was retained in the sinus and there were scattered deposits in lymph spaces from the zygoma to the clavicle, including the submental and sublingual regions. Films made 1 year later showed relatively little change in distribution but some general reduction. The author considered the case interesting in showing that upward drainage occurs, that lipiodol does not accumulate in the lymph nodes and that elimination of the drug by absorption may be extremely slow.

Giant-cell Bone Tumor.—PEIRCE (*Am. J. Roent. and Rad. Therap.*, 1932, **28**, 167) reports the results of treatment in 14 cases. In his opinion, Roentgen irradiation in repeated and relatively moderate doses offers the most for the patient, except when for cosmetic or functional reasons better results can be obtained by the addition of surgical intervention; but this should not follow Roentgen therapy short of 6 weeks or more. If surgery is contemplated thorough chemical cauterization of the cavity should be executed, followed immediately by a consistent program of Roentgen therapy.

NEUROLOGY AND PSYCHIATRY

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A Contribution to the Study of Truancy.—BROADWIN (*Am. J. Orthopsychiat.*, 1932, **3**, 253) states that truancy is to be considered merely as one aspect of the total personality in its adjustment or maladjustment to the total situation. The study of the problem of truancy may open to us important personality disorder which might otherwise go unsuspected. It requires a study of the child and his unconscious psychic life, his instinctual strivings, their evolution and forms of expression. There are many generally accredited reasons for truancy, as loss of interest because of backwardness, bad associates, and so forth. Reasons of such character do not express the problem in terms of the deeper personality factors. "Since the school situation is in many respects a substitute for the situation in the home, one must seek a relationship between the adjustment in the home and the adjustment in the school. Truancy from school may then have its correlation in behavior symptoms in the home. It may represent an act of defiance, an attempt to obtain love, or escape from real situations to which it is difficult to adjust." This article describes a form of truancy occurring in the child who is suffering from a deep-seated neurosis of the obsessional type or who displays a neurotic character of the obsessional type. The truancy is part of the general symptomatology and part of the multiplicity of personality difficulties which have received little corrective attention. In the typical case the child is absent for periods varying for several months to a year. The parent knows where the child is, that is, hear the mother or home. The truancy is not understood by the parents or school. The child may say that it is afraid to go to school, afraid of the teacher, or says it does not know why it won't go to school. At home it is happy and carefree; at school it is fearful, miserable and runs away at the first chance. In the course of treatment the child eventually feels free to discuss problems. Obsessive ideas are revealed, such as the death of the mother or that the house is on fire, and so forth. The child feels that he must run home. Then he fears the return to school because of "terrible feeling" when these ideas come to his head. He would not tell these ideas before because they are "crazy ideas" and people might think him "crazy." The reasons obtained from the child are meaningful in that they indicate the strong infantile love attachment to the mother and the intensive sadistic or hostile attitude towards her, which underlie the anxiety. "There is conflict between the primitive instinctual drives which demand expression and the ego . . . The symptom implies a gratification of the prohibited instinctual drives and at the same time contains the elements

of self-punishment to mollify the super ego. The punishment is expressed as the anxiety or the disability borne by the patient." Two typical cases are presented and discussed in a moderate amount of detail. Conclusions are that the understanding and treatment of these cases and other cases of truancy "can most effectively be approached through the handling of the unconscious psychic life of the patient, the evolution of the love and hate instincts. It is in the light of this that one can feel that the best results would be obtained from classical child analysis. However, we all know that at present such a procedure is not practicable in child guidance clinics. One then must employ a modified form of approach. Although one can feel that an improvement is brought about, the question remains open as to whether deep inroads are made on the basic neurosis by the clinic procedure."

PATHOLOGY AND BACTERIOLOGY

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Osteitis Fibrosa.—A short review of the earlier and more recent work on osteitis fibrosa together with conclusions of original studies have been reported by LAND (*Am. J. Path.*, 1932, **8**, 263). Attention is called to the observations of Pommer who regarded cyst formation dependent upon hemorrhage following trauma. The resulting congestion and inflammatory response along with chronic irritation produced by functional activity leads to a resorption and atrophy of the surrounding bone, a sclerosing process in the marrow, and the formation of new bone with secondary hemorrhage and progressive cyst formation. This is most commonly seen following injury to the epiphysis in the young, the hemorrhage and edema remaining localized if the periosteum is still intact. The resorptive and sclerosing process is compared to the induration in parenchymatous organs following chronic passive congestion, similar changes also being seen in callus formation, secondary new growths and tuberculous and syphilitic bone lesions. Studies concerning the relationship between osteomalacia, osteitis fibrosa and rickets reveal that those parts of the skeleton most subject to strain yield because of insufficient calcification. In these conditions congestion of the blood and lymph vessels, with continuous mechanical irritation, may lead to osteitis fibrosa. The recent experimental production of this lesion by Jaffe, Bodansky and Blair through the administration of parathormone, and the occasional association of osteitis fibrosa with hyperplasia or tumors of the parathyroid glands do not invalidate the above conception, the vascular disturbances being secondary to the action of functional trauma on softened bone.

The Pathology of Aneurysm: A Review of 167 Autopsies.—GARLAND (*J. Path. and Bact.*, 1932, **35**, 333) makes a statistical study of the cases of aneurysm occurring in 12,000 autopsies at the Leeds General Infirmary and the findings are compared with similar studies in the literature. One or more aneurysms were found in 167 cases. Aneurysm of the thoracic aorta was found in 78 cases; 7 cases showed 2 aneurysms and 1 case 3, making a total of 87 thoracic aortic aneurysms. Aneurysm of the ascending aorta was the most common and was present in 34 cases. The corrected ratio of incidence for males and females was 1.75 to 1. Saccular aneurysms were the most common type encountered. The majority of the aneurysms were syphilitic in origin. Two appeared to be atheromatous and 2 were infective. Thirty-three per cent ruptured into the pericardium. Four cases of aneurysm of the sinuses of Valsalva were found, 2 being mycotic and 2 syphilitic. The average age for thoracic aortic aneurysms coming to autopsy was 53 years. Death was due to rupture of the aneurysm in 36 cases, to pressure effects in 27 and unrelated to the aneurysm in 18. Sixteen cases of abdominal aortic aneurysm were encountered, 7 were syphilitic and 9 atheromatous. The average age at autopsy was 65 years. There were 32 cases of cerebral aneurysm. The author points out that many cerebral aneurysms are probably missed. Death resulted from rupture of the aneurysm in 84.3 per cent of the cases. Most of the aneurysms were smaller than a pea. The most common site was the right middle cerebral artery, where 10 aneurysms were situated. Fourteen aneurysms were associated with gross arterial disease, usually atheroma, and 5 were syphilitic. Only 1 aneurysm of the "miliary" type was found and that was in an advanced arteriopathy. There were 28 cases of aneurysms of the heart, 21 of which were in the left ventricle. In 1 case there was a minute aneurysm of the right coronary artery associated with atheroma. Four cases showed aneurysm of the mitral or aortic valves associated with endocarditis. Of the small vessels aneurysms of the splenic artery were the most numerous after the cerebral arteries. Five cases were found all due to atheroma. Three cases of renal aneurysm were found, 2 of which were probably syphilitic. The rarity of renal aneurysm is stressed. Twelve cases of peripheral aneurysms were syphilitic, mycotic, atheromatous or traumatic. In summing up the causes of aneurysm the author considers that the large proportion of cerebral aneurysms in the first half of life are congenital in origin. Trauma was found to be a rare cause of aneurysm. Syphilis was found to be the most important single cause of aneurysm, producing 91.3 per cent of thoracic aortic aneurysms. Embolism as a cause of aneurysm was almost always associated with infectious processes, the most common infection being infective endocarditis. In many cases no vascular abnormality but atheroma was found as a cause of aneurysm. Atheroma was also found in association with other abnormalities as a contributory cause of aneurysm.

The Occurrence of True Bone Within a Renal Calculus.—STUART and KRIKORIAN (*J. Path. and Bact.*, 1932, **35**, 373) report the occurrence of true bone within a renal calculus. Several stones were evacuated at operation from the kidney of a female, aged 22 years, who had a definite history of pyelitis and nephrolithiasis for at least 6 years.

Six stones were examined. The stones contained 70 to 80 per cent calcium oxalate and 6 per cent calcium phosphate. Five of the stones showed nothing unusual. The sixth stone was bilobed and was the shape of an acorn. A tag of fibrous tissue was seen entering a small foramen at the junction of the two lobes of the stone. The tag of tissue was evidently a pedicle torn from its attachment to the kidney pelvis. Section of the stone revealed a central cavity filled with a gritty white substance from which blood exuded. On microscopic section the central core was found to consist of compact and cancellated osseous tissue as well as a periosteum-like membrane adjacent to the compact portion. Numerous capillaries and spaces for fat and marrow tissue were also seen. The rarity of the condition is emphasized and 2 similar cases reported by PHEMISTER (*Ann. Surg.*, 1923, **77**, 135), the only cases to be found in the literature, are quoted. In explaining the vicarious osteogenesis reference is made chiefly to the work of HUGGINS (*Arch. Surg.*, 1931, **22**, 377), who showed a clear relationship between proliferating epithelium in the kidney pelvis of dogs and the formation of bone in the mucosal stroma. The theory is postulated that infection in the kidney pelvis leads to the proliferation of epithelial buds and that bone formation begins in the fibrous core of such buds. Continuation of the process leads to a greater formation of bone and the eventual erosion of the covering epithelium. The bone then connected by a fibrous pedicle to the kidney tissue forms a nidus for the deposition of calcium salts from the urine.

The Interstitial Reactions Caused by Various Dusts and Their Influence on Tuberculous Infections.—KETTLE (*J. Path. and Bact.*, 1932, **35**, 395) injected 0.5 to 1 cc. of 1 to 3 per cent suspensions of various silicious and nonsilicious dusts into the flanks of a series of mice. The animals were killed at varying intervals and sections were made of the local lesion. The characteristic feature of the lesions produced by nonsilicious dusts was their quiescence. There was only a slight transient cellular reaction. Amorphous, colloidal and crystalline silica, mine dust containing silica, shale, kaolin and asbestos, all produced a local coagulative necrosis accompanied by a marked cellular reaction. Carborundum, a silicious dust, and silica encrusted with iron oxid were inert and produced a lesion similar to the nonsilicious dusts. In order to test the effect of the dusts upon a tuberculous infection a batch of mice were inoculated into the right and left flanks with suspensions of two of the dusts to be tested, and after an interval (usually 24 hours) an emulsion of living tubercle bacilli was injected into the general circulation by way of the tail vein. The mice tolerated heavy doses of the bacilli, and 0.33 to 0.5 cc. of an emulsion containing 500,000 bacilli per cc. was used. The animals were killed at varying intervals and the general bodily seeding of bacilli and the numbers of bacilli in the dust-produced lesions were estimated by stained sections. The distribution of the organisms throughout the body was satisfactorily constant. An occasional mouse showed an unduly heavy seeding and had to be discarded. It was found that the inert or nonsilicious dusts had a neutral effect on the progress of the interstitial tuberculous lesions, while the active or silicious dusts with the exception of carborundum and silica coated with ferric oxid had a positive influence.

The numbers of bacilli varied greatly from lesion to lesion, but there was a great preponderance of organisms in the active silicious lesions. The present methods of producing pneumoconiosis in laboratory animals, by exposing them to dusty atmospheres, is too laborious and takes too long—2 years or more—to be of great practical value. The author suggests the injections of suspensions of dust into the interstitial tissues as a useful and dependable method for the determination of the pathogenicity of atmospheric pollutions in various industries.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Etiology of Dental Caries.—There are, in general, two conflicting views in regard to the etiology of caries of the deciduous as well as of the permanent teeth. The one, older and better entrenched, holds that dental caries is due mainly to local conditions, to peculiar configurations of the occlusal surface or to an abnormal environment within the mouth which invites decay. The other view is that caries is essentially a systemic disturbance and that local factors are of secondary significance. HESS and ABRAMSON (*Dental Cosmos*, 1931, **73**, 849) report the results of the examination of two groups of children who had been closely observed during infancy (some 6 or 7 years ago). One group was known to have been free from rickets and the other to have had the disease in mild or moderate form during the first year of life. It was found that the children who had been protected from rickets had developed less caries than those who had not been protected. Nevertheless, numerous instances of dental caries were found in the nonrachitic group. The deciduous teeth as well as the first molars were involved. Considerable caries was likewise observed in the teeth of a group of children who had been breast-fed and had shown no evidence of rickets in a study carried out in 1922 and 1924. An average degree of caries was found in the teeth of children whose mothers were given cod-liver oil during the latter months of pregnancy; this group likewise had been studied for rickets about 7 years ago. A consideration of the geographic distribution of dental caries brought about the fact that it is rampant among the children and adults in the subtropics and tropics, for example, in Florida, Hawaii, Jamaica and Trinidad. This distribution constitutes a strong argument against regarding rickets as the essential etiologic factor of dental caries. A similar consideration of geographic distribution argues against the acceptance of scurvy as

an important causal factor of caries, which is present in marked degree where fruit and vegetables are in greatest abundance and, on the other hand, is least prevalent in countries, such as Alaska and Greenland, where antiscorbutic foods are scarce. An analysis of clinical conditions likewise indicates that dental caries cannot be attributed to a deficiency of vitamins A or B. Pathologic lesions of the enamel are by no means infrequent among young children. This is a disorder quite distinct from caries and involves particularly the upper incisor teeth. It is found in the deciduous teeth of children who have had neither rickets nor scurvy. As has been shown by others, there is often an association between this disorder, infantile tetany and a deficiency of calcium in the blood. A relationship exists between the growth and the occurrence of caries and more particularly between development and caries. This is clearly brought out by plotting a curve of incidence of caries and noting the exceptionally high incidence at the period of adolescence and the years immediately succeeding.

Diphtheria Antibodies Transmitted from Mother to Child.—Neill and coworkers (*J. Immunol.*, 1932, **22**, 117) made measurements of the diphtheria antibodies in the blood of a mother and baby during the 18 months following the birth. Tests were made for antibodies of the antibacterial sort as well as for the antitoxin. The antibacterial antibodies were found in the serum of the baby over the period in which placentally transmitted antibodies could be expected to be retained, but owing to their passive origin they were absent in later bleedings. Control tests showed that the antibacterial antibodies were absent in the sera of babies whose mothers did not possess them. The data of the antitoxin tests owe their interest to the high degree of immunity of the mother and to the length of time over which the blood of both baby and mother was studied.

The Relation of Bovine Mastitis to Human Infection.—Brooks (*J. Prev. Med.*, 1932, **6**, 111) points out that mastitis is common among dairy cattle and the infection is readily communicated from one cow to another. The types of streptococci which are the common incitants apparently are not infective for man, but when present in milk in large numbers with their toxins may be responsible for severe toxic disturbances, especially in children. Organisms of animal or human origin, pathogenic for man, may be present in diseased udders. These include the tubercle bacillus, Brucella abortus, and the hemolytic streptococci which are incitants of septic sore throat and scarlet fever. Udders infected with Brucella abortus may excrete the organisms during the life of the animal. Agglutination and complement-fixation tests on milk from infected quarters have given positive results, that from uninfected quarters negative. Agglutinating power in the blood may be due to infection localized in the udder. Several milk-borne epidemics of septic sore throat in upper New York State have been traced to raw milk from herds with cases of mastitis. In the more recent epidemics hemolytic streptococci corresponding to those found in the human cases have been obtained from the infected udders. Recent experience suggests the desirability of persistent effort to find the infected cows. One epidemic of scarlet fever in 1922 was traced to

raw milk, including that from a cow with mastitis from which hemolytic streptococci were obtained. Experience suggests that organisms from human sources are primarily responsible. Since January 1, 1924, 6 outbreaks of gastroenteritis have been traced to raw milk from herds in which there were cases of mastitis. In 3 of these most of the patients were children given the milk in school. Illness developed within 4 or 5 hours. Cows with chronic mastitis were involved and common types of nonhemolytic streptococci isolated. Bovine mastitis is a major problem in prevention of milk-borne infection. A slowly developing movement for eradication offers no practical and immediate solution, nor will careful dairying methods and inspection afford adequate protection. Pasteurization is the only practical safeguard.

A Study of Certain Epidemiologic Factors in the Pneumonia of Children.—SHULTZ (*Am. J. Hyg.*, 1932, **15**, 80) determined the incidence of pneumococcus carriers by cultures from the throats of 86 individuals, representing the families of 21 children with pneumococcus pneumonia. In 11 carriers, or 12.7 per cent, of those studied, the type of pneumococcus found was the same as that isolated from the pneumonia patient. The virulence of the pneumococcus from several cases was compared with the virulence of the strains isolated from the corresponding carriers. There was no significant variation. The virulence of Type I organisms obtained from cases and carriers was higher than the virulence of Types III or V isolated from the cases. The duration of carrier state was followed in 35 convalescent children and was found to vary between 2 and 152 days. Types I and III remained in the pharynx for a longer period of time than Type II or the subdivisions of Group IV. The pneumococci found to replace the infecting types did not differ greatly from those found in the pharynx of the healthy contact. The unclassified pneumococcus which apparently replaced the infecting type might in some instances have been a degraded form of the original strain. Two children who developed symptoms of pneumonia in the hospital were studied from the viewpoint of ward infection. The sources of the infections could not be traced. The author concludes that until further study increases our knowledge of the factors involved in the etiology of pneumonia, preventive measures can only be directed toward the epidemiologic control of the suspected modes of transmission in children—healthy carriers and convalescent patients.

Milk-borne Septic Sore Throat and Scarlet Fever and Their Relation to Beta Hemolytic Streptococci.—WILLIAMS and GURLEY (*J. Bacteriol.*, 1932, **23**, 241) give a short review of the present status of "Streptococcus epidemicus" as a species and present evidence to show that neither of the characteristics claimed as the only species characteristics—capsule formation and moist growth on blood media—holds sufficiently to be used in designating a species and that at present strains of hemolytic streptococcus from septic sore throat not otherwise placed by agglutinin absorption should be termed simply Streptococcus hemolyticus. Strains of hemolytic streptococci from milk-borne epidemics of scarlet fever and of septic sore throat and from other sources have been studied to determine their serologic relationship to our type strains from scarlet fever and erysipelas and to each other. The strains from septic sore

throat in the 3 Massachusetts outbreaks of 1928 were shown to fall by agglutinin absorption partly into the largest scarlet fever group Type I and Subtype I and partly into 2 other groups. These 2 newly discovered agglutinative groups have been called epidemicus (or septic sore throat) Type I and epidemicus (or septic sore throat) Type II. Septic sore throat strains and scarlet fever strains may occur in the same epidemic, composed of cases classed mostly as scarlet fever. A scarlet fever type of organism may be recovered from cases recorded clinically as constituting a septic sore throat outbreak. Exotoxins of similar quality as regards their neutralization ability, but of varying quantity, have been produced by all of these type strains. The authors conclude from their studies that milk-borne epidemics of septic sore throat and of scarlet fever may be caused, respectively, by one or several agglutinative types of hemolytic streptococci. When scarlet fever predominates, usually the epidemic strain belongs to one of the common scarlet fever agglutinative types; when septic sore throat predominates, the epidemic strain may be one of several agglutinative types, respectively, 2 of which have been demonstrated in these studies and have been called tentatively epidemicus agglutinative Type I and epidemicus agglutinative Type II.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 21, 1932

Some Effects of Alpha Radiation on Cells.—R. E. ZIRKLE (Botanical Laboratory, University of Missouri). The properties of α rays make possible a great simplification of the system in the study of the effects of ionizing radiation on living cells. Polonium was used as source of α rays because it emits other rays to no significant degree and because of its convenience. Spores of the fern Pteris longifolia were irradiated because they can be handled in the air-dry condition and do not require aseptic culture methods. Three distinct processes connected with germination—cracking of wall, development of chlorophyll and cell division—are inhibited by α rays. The susceptibility of these processes increases in the order named. The doses required to produce 50 per cent inhibition of these processes are, respectively, 4000, 13,000 and 33,000 α particles per protoplast. These doses correspond to energy of the order 10^{-6} ergs per μ^3 absorbed by the protoplast. This is of the order of $\frac{1}{10}$ the energy per μ^3 calculated by others for 50 per cent inhibition of cell division in yeast. When a dose capable of producing 50 per cent inhibition of division is used, from 7 to 16 per cent of the protoplast is liable to direct alteration by ionization. When a dose capable of producing 50 per cent cracking is used, more than half and possibly all of the protoplast is liable to such direct alteration. Irradiation of definite fractions of the protoplast indicates the following conclusions: (*a*) Cracking, greening and division may each be inhibited

by extranuclear injury, but all are much more easily inhibited if the nucleus is irradiated. (*b*) The extranuclear injury which inhibits greening is not direct injury to plastids or proplastids. (*c*) Imbibition is inadequate for production of cracking in the normal spore. (*d*) Nuclear injury is a function of energy absorbed rather than of number of incident α particles.

A Study of the Influence of Electric Current Upon Nerves Growing in Tissue Culture.—S. C. Williams (Laboratory of Anatomy, University of Pennsylvania). Nerve cells and fibers from pieces of brain from 4- to 8-day incubated chick embryos cultivated *in vitro* in Tyrode-diluted chicken blood plasma with added embryonic extract were placed by means of a micromanipulator between silver-silver chlorid-Ringer-Ringer agar microelectrodes in a warm moist chamber. Electric current, of density 130 to 0.2 milliampere per square millimeter of average cross-sectional area of the tip of the electrodes, was applied for periods up to 20 minutes. Observations on more than 100 experiments show a formation of granules in the cytoplasm, a softening and retraction from the cathode with occasional formation of short temporary pseudopodia and generally a movement toward the anode. Strong current is quickly lethal; weaker current is now being used and its effects over longer periods of time studied. This work was done in part in collaboration with Dr. T. Petérfi at the Kaiser-Wilhelm Institute für Biologie in Berlin, and with the assistance of a grant from the Faculty Research Committee of the University of Pennsylvania.

The Anion Cation Content of Normal and Infected Gall Bladder Bile.—C. G. Johnston, I. S. Ravdin, C. Riegel and J. H. Austin (Laboratories of Surgical Research and Research Medicine, University of Pennsylvania). We have previously reported the anion cation concentrations of certain constituents in normal dog's hepatic and gall bladder bile. When the gall bladder is normal it alters hepatic bile by concentrating the calcium, bile salt and base. The chlorid and total CO_2 concentrations decrease and the pH is reduced. Fluid is always absorbed. When the gall bladder becomes damaged fluid pours into the gall bladder. Base remains as in hepatic bile, while bile salts and calcium decrease in concentration and chlorid and total CO_2 increase in concentration. The pH is increased. Normal human gall bladder bile is similar to normal dog gall bladder bile in its concentrations of the substances studied. Studies of human bile removed from the diseased gall bladder at operation have now been made. Changes similar to those obtained in the dog when the gall bladder is infected have been observed. Roughly the data from the diseased gall bladder are divisible into 3 groups on the basis of chemical analyses and the ability of the gall bladder to concentrate its contents as evidenced after the administration of sodium tetraiodophenolphthalein. With increasing damage there is a tendency for a reduction of bile salts and calcium and an increase in chlorid and total CO_2 concentrations, until in the nonvisualized gall bladder containing stones bile salts, as demonstrated by the Gregory-Pascoe reaction, are frequently absent, while chlorid is above the blood level and calcium is present in approximately the same concentration as found in hepatic bile. Between normal human

gall bladder bile and that found in the severely damaged gall bladder one finds bile in which the bile salt concentration decreases with increasing histologic evidence of disease.

The Colorimetric Estimation of Chlorids in Blood and Urine.—B. B. WESTFALL (Laboratory of Pharmacology, University of Pennsylvania). When silver chromate is suspended in an alkali chlorid solution silver chlorid and alkali chromate are formed in stoichiometric proportions. The concentration of chlorid in a solution can therefore be determined by adding powdered silver chromate, stirring, filtering and estimating the liberated chromate in the filtrate. Estimation of chromate can be accomplished with great accuracy by mixing with Cazeneuve's reagent (s-diphenylcarbazid) whereupon an intense purple-red color is produced. The color production follows Beer's law over a satisfactory range. Standard sodium chlorid solutions or standard sodium chromate solutions may be used for the production of standard colors with which comparison is made. The color produced is so intense that very small amounts of chlorid can be estimated.

A micro modification of the method was described by which it is possible to determine the chlorid content of 0.0001 cc. containing as little as 0.0004 mg. sodium chlorid, with an average error of about 3 per cent.

The Chlorid Content of Glomerular Urine and Plasma From Frogs.—B. B. WESTFALL and A. N. RICHARDS (Laboratory of Pharmacology, University of Pennsylvania). In a series of 11 consecutive experiments glomerular urine and blood plasma were collected from normal frogs and analyzed for chlorid by the method described above. The greatest difference found in chlorid content of the 2 fluids was 6 per cent; the average difference was less than 2 per cent. The conclusion is that in respect of chlorid, glomerular urine in frogs is an ultrafiltrate from plasma.

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